## ATENT COOPERATION TREATY

1211 Geneva 20, Switzerland Pascal Piriou 34, chemin des Colombettes The International Bureau of WIPO Authorized officer Rule 32.2(b). made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under 2. The election in a notice effecting later election filed with the International Bureau on: 16 February 2001 (16.02.01) IN the demand filed with the International Preliminary Examining Authority on: The designated Office is hereby notified of its election made: HILLMAN, Jennifer, L. et al Applicant (00.70.12) 000S ylul 1S (66.70.1S) 6661 YIUL 1S International filing date (day/month/year) Priority date (day/month/year) PCT/US00/19948 PF-0722 PCT International application No. Applicant's or agent's file reference 30 May 2001 (30.05.01) in its capacity as elected Office Date of mailing (day/month/year) **ETATS-UNIS D'AMERIQUE** Arlington, AV 22202 CP2/5C24 2011 South Clark Place Room (PCT Rule 61.2) Office, PCT United States Patent and Trademark **NOTIFICATION OF ELECTION** US Department of Commerce Commissioner PCT From the INTERNATIONAL BUREAU

Telephone No.: (41-22) 338.83.38

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Facsimile No.: (41-22) 740.14.35

#### From the INTERNATIONAL BUREAU

HAMLET-COX, Diana Incyte Genomics, Inc. 3160 Porter Drive Palo Alto, CA 94304 ETATS-UNIS D'AMERIQUE

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# NOTIFICATION CONCERNING OF PRIORITY DOCUMENT OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

	INCYTE GENOMICS, INC. et al
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1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document which is reasonable under the circumstances.

The !ofters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau, Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

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ized officer Taleb AKREMI	OVIPA  The International Bureau of WIPO  34, chemin des Colombettes  Seneva 20, Switzerland





#### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

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		. Applicant
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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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## nternational Application No PCT/US 00/19948

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#### INTERNATIONAL SEARCH REPORT

Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.
4. (A) required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  See further information sheet invention group 1.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
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Decause they relate to subject matter not required to be searched by this Authority, namely:  Claims Mos.:  Claims Nos.:  Claims Mos.:  Claims Mos.:  Claims Mos.:  Claims Mos.:  Claims Mos.:  Claims Mos.:  Box II Observations where unity of inventions in this international application, as follows:  This International Searching Authority found multiple inventions in this international application, as follows:



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(54) Title: CELL CYCLE AND PROLIFERATION PROTEINS



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#### CETT CACLE AND PROLIFERATION PROTEINS

#### TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of cell cycle and proliferation proteins and to the use of these sequences in the diagnosis, treatment, and prevention of immune, developmental, and cell signaling disorders, and cell proliferative disorders including cancer.

#### BYCKCKOUND OF THE INVENTION

Cell division is the fundamental process by which all living things grow and reproduce. In unicellular organisms such as yeast and bacteria, each cell division doubles the number of organisms, while in multicellular species many rounds of cell division are required to replace cells lost by wear or by programmed cell death, and for cell differentiation to produce a new tissue or organ. Details of the cell division cycle may vary, but the basic process consists of three principal events. The first essential proteins. In the second event, mitosis, the nuclear material is divided and separates to opposite sides of the cell. The final event, cytokinesis, is division and fission of the cell cytoplasm. The sequence and timing of cell cycle transitions are under the control of the cell cytoplasm.

System which controls the process by positive or negative regulatory circuits at various check points. Mitosis marks the end of interphase and concludes with the onset of cytokinesis. There are

telophase. Prophase includes the formation of bi-polar mitotic spindles, composed of mictrotubules and associated proteins such as dynein, which originate from polar mitotic centers. During and associated proteins such as dynein, which originate from polar mitotic centers. During and associated proteins such as dynein, which originate from polar mitotic centers. During attachment to the mitotic spindles. The ensuing movement of the nuclear material to opposite poles along the mitotic spindles occurs during anaphase. Telophase includes the disappearance of the mitotic spindles and kinetochore fibers from the nuclear material. Mitosis depends on the interaction of numerous proteins. For example, mutation studies in the Drosophila melanogaster zw10 gene show a disruption in chromosome segregation. ZW10 protein appears to function at the kinetochore as a tension-sensing checkpoint during the onset of anaphase. ZW10 appears to have a direct role in the recruitment of dynein to the kinetochore, and, dynein's involvement in the coordination of chromosome separation at the onset of anaphase and/or poleward movement (Starr, D.A. et al. (1998) tension-sensing checkpoint during the onset of anaphase and/or poleward movement (Starr, D.A. et al. (1998)).

Regulated progression of the cell cycle depends on the integration of growth control pathways with the basic cell cycle machinery. Cell cycle regulators have been identified by selecting for human and yeast cDNAs that block or activate cell cycle arrest signals in the yeast mating

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pheromone pathway when they are overexpressed. Known regulators include human CPR (cell cycle progression restoration) genes, such as CPR8 and CPR2, and yeast CDC (cell division control) genes, including CDC91, that block the arrest signals. The CPR genes express a variety of proteins including cyclins, tumor suppressor binding proteins, chaperones, transcription factors, translation factors, and RNA-binding proteins (Edwards, M.C. et al. (1997) Genetics 147:1063-1076).

The human CDC protein, CDC23, is homologous to the <u>S. cerevisiae</u> protein CDC23 which

functions in the transition from metaphase to anaphase as well as in the exit from mitosis (Zhao, N. et al. (1998) Genomics 53:184-190). The <u>C. elegans</u> gene cullin-1 (cul1) is a negative regulator of the cell cycle. cul1 regulates the G1 to 5 phase transition and <u>C. elegans</u> cul1 mutants exhibit hyperplasia of all tissues through acceleration of this transition by overriding mitotic arrest. cul1 is a member of a conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell 85:929-839).

Several cell cycle transitions, including the entry and exit of a cell from mitosis, are dependent upon the activation and inhibition of cyclin-dependent kinases (Cdks). The Cdks are composed of a kinase subunit, Cdk, and an activating subunit, cyclin, in a complex that is subject to many levels of regulation. There appears to be a single Cdk in <u>Saccharomyces cerevisiae</u> and binding to and activating cyclin-dependent protein kinases which then phosphorylate and activate negatively regulated by phosphorylation, and by targeted degradation involving molecules such as such as such regulated by phosphorylation, and by targeted degradation involving molecules such as such as Suc1 that modify their specificity or accessibility to regulators (Patra, D. and W.G. Dunphy such as Suc1 that modify their specificity or accessibility to regulators (Patra, D. and W.G. Dunphy levels and construction).

The male and female reproductive systems are complex and involve many aspects of growth and development. The anatomy and physiology of the male and female reproductive systems are reviewed in Guyton, A.C. ((1991) <u>Textbook of Medical Physiology</u>, W.B. Saunders Co., Philadelphia

The male reproductive system includes the process of spermatogenesis, in which the sperm are formed. Male reproductive functions are regulated by various hormones. The hormones exert their effects on accessory sexual organs, and are involved in cellular metabolism, growth, and other bodily functions.

Spermatogenesis begins at puberty as a result of stimulation by gonadotropic hormones

released from the anterior pituitary. Immature sperm (spermatogonia) undergo several mitotic cell divisions before undergoing meiosis and full maturation. The testes secrete several male sex hormones. Testosterone, the most abundant, is essential for growth and division of the immature sperm, and for the masculine characteristics of the male body. Three other male sex hormones,

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gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), control sexual function.

system. The ovaries and uterus are the source of ova and the location of fetal development, respectively. The fallopian tubes and vagina are accessory organs attached to the top and bottom of the uterus, respectively. Both the uterus and ovaries have additional roles in the development and loss of reproductive capability during a female's lifetime. The primary role of the breasts is lactation. Multiple endocrine signals from the ovaries, uterus, pituitary, hypothalamus, adrenal glands, and other tissues coordinate reproduction and lactation. These signals vary during the monthly

The uterus, ovaries, fallopian tubes, vagina, and breasts comprise the female reproductive

menstruation cycle and during the female's lifetime. Similarly, the sensitivity of reproductive organs to these endocrine signals varies during the female's lifetime.

A combination of positive and negative feedback to the ovaries, pituitary and hypothalamus

glands controls physiologic changes during the monthly ovulation and endometrial cycles. The anterior pituitary secretes two major gonadotropin hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), regulated by negative feedback of steroids, most notably by ovarian estradiol. If fertilization does not occur, estrogen and progesterone levels decrease. This sudden reduction of the ovarian hormones leads to menstruation, the desquamation of the endometrium. Hormones further govern all the steps of pregnancy, parturition, lactation, and menopause.

During pregnancy large quantities of human chorionic gonadotropin (hCG), estrogens, progesterone, and human chorionic somatomarmotropin (hCS) are formed by the placenta. hCG, a glycoprotein similar to luteinizing hormone, stimulates the corpus luteum to continue producing more progesterone and estrogens, rather than to involute as occurs if the ovum is not fertilized. hCS is similar to growth hormone and is crucial for fetal nutrition.

The female breast also matures during pregnancy. Large amounts of estrogen secreted by the placenta trigger growth and branching of the breast milk ductal system while lactation is initiated by

Parturition involves several hormonal changes that increase uterine contractility toward the end of pregnancy, as follows. The levels of estrogens increase more than those of progesterone. Oxytocin is secreted by the neurohypophysis. Concomitantly, uterine sensitivity to oxytocin increases. The fetus itself secretes oxytocin, cortisol (from adrenal glands), and prostaglandins.

Menopause occurs when most of the ovarian follicles have degenerated. The ovary then

produces less estradiol, reducing the negative feedback on the pituitary and hypothalamus glands. Mean levels of circulating FSH and LH increase, even as ovulatory cycles continue. Therefore, the ovary is less responsive to gonadotropins, and there is an increase in the time between menstrual cycles. Consequently, menstrual bleeding ceases, and reproductive capability ends.

Differentiation and Proliferation

the secretion of prolactin by the pituitary gland.

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Tissue growth involves complex and ordered patterns of cell proliferation, cell



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differentiation, and apoptosis. Cell proliferation must be regulated to maintain both the number of cells and their spatial organization. This regulation depends upon the appropriate expression of proteins which control cell cycle progression in response to extracellular signals, such as growth factors and other mitogens, and intracellular cues, such as DNA damage or nutrient starvation. Molecules which directly or indirectly modulate cell cycle progression fall into several categories, including growth factors and their receptors, second messenger and signal transduction proteins, oncogene products, tumor-suppressor proteins, and mitosis-promoting factors.

Embryogenesis is a process in which distinct patterns of protein expression control proper development. This process involves a host of proteins each with distinct and highly coordinated expression of two related genes Mag1 and Mrg1 contribute to normal embryonic development. Mag1 is expressed in the posterior domains of the developing mesoderm, while Mrg1 is expressed in the anterior visceral endoderm. Properly coordinated expression of each protein throughout embryogenesis is critical for proper tissue and organ formation (Dunwoodie, S.L. et al. (1998) Mech. Dev. 72:27-40).

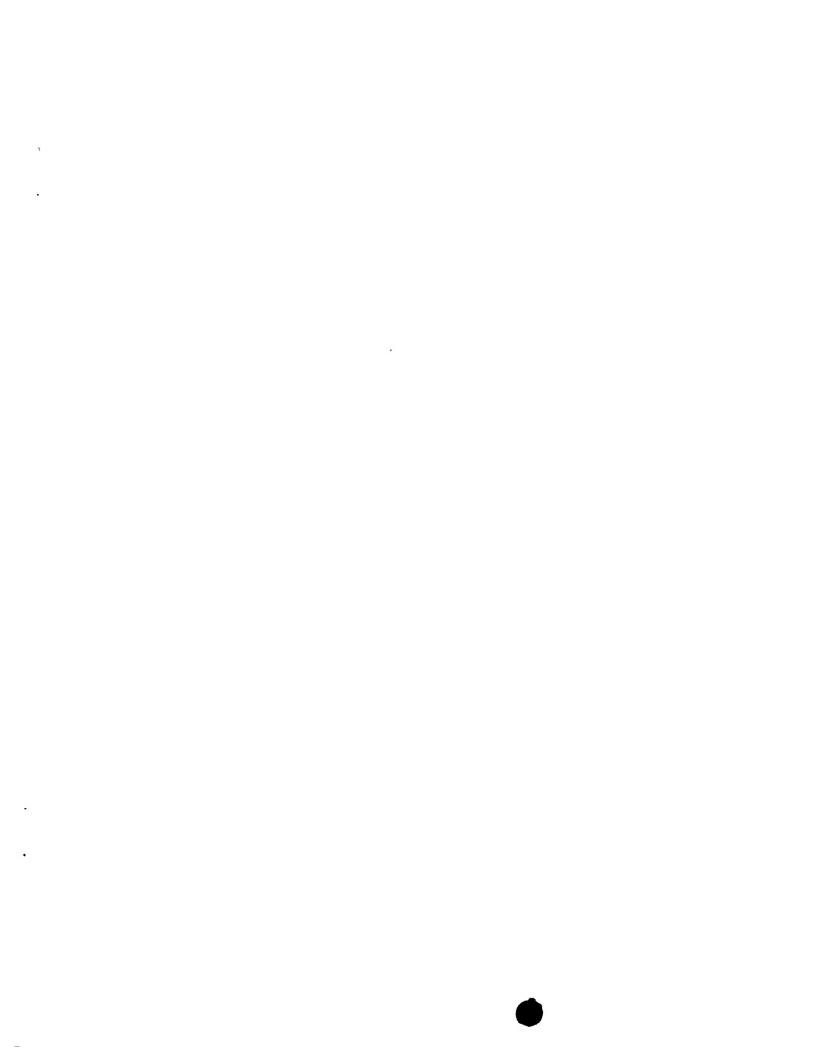
Growth factors were originally described as serum factors required to promote cell

proliferation. Most growth factors are large, secreted polypeptides that act on cells in their local environment. Growth factors bind to and activate specific cell surface receptors and initiate intracellular signal transduction cascades. Many growth factor receptors are classified as receptor tyrosine kinases which undergo autophosphorylation upon ligand binding. Autophosphorylation or SH3 domains (Src homology regions 2 or 3). These proteins then modulate the activity state of small G-proteins, such as Ras, Rab, and Rho, along with GTPase activating proteins (GAPs), guanine nucleotide releasing proteins (GARPs), and other guanine nucleotide exchange factors. Small G proteins act as molecular switches that activate other downstream events, such as mitogen-activated protein kinase (MAP kinase) cascades. MAP kinases ultimately activate transcription of mitosis-

In addition to growth factors, small signaling peptides and hormones also influence cell proliferation. These molecules bind primarily to another class of receptor, the trimeric G-protein coupled receptor (GPCR), found predominantly on the surface of immune, neuronal and reuroendocrine cells. Upon ligand binding, the GPCR activates a trimeric G protein which in turn triggers increased levels of intracellular second messengers such as phospholipase C, Ca<sup>2+</sup>, and cyclic secretion or breakdown of other signaling pathways indirectly promote cell proliferation by causing the secretion or breakdown of other signaling molecules that have direct mitogenic effects. These signaling cascades often involve activation of kinases and phosphatases. Some growth factors, such as some members of the transforming growth factor beta (TGF- $\beta$ ) family, act on some cells to stimulate cell proliferation and on other cells to inhibit it. Growth factors may also stimulate a cell at one concentration and inhibit the same cell at another concentration. Most growth factors also have a one concentration and inhibit the same cell at another concentration. Most growth factors also have a

promoting genes.

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and the types of stimuli acting on the cell (Smith, A. et al. (1994) Cell 76:959-962; and Nocentini, G. of cell, its stage of differentiation and transformation status, which surface receptors are stimulated, cell death, as well as regulate proliferation and differentiation. The cell response depends on the type For example, the tumor necrosis factor/nerve growth factor (TNF/NGF) family can activate or inhibit proliferation, survival, differentiation, migration, or function of cells depending on the circumstance. multitude of other actions besides the regulation of cell growth and division: they can control the 117/0/10 OM

Neighboring cells in a tissue compete for growth factors, and when provided with "unlimited" et al. (1997) Proc. Natl. Acad. Sci. USA 94:6216-6221).

A. (1997) Cell Tissue Res. 290:331-341). provide stimulatory/anti-adhesive or inhibitory properties, respectively, for axonal growth (Faissner, may act as growth factors. Tenascin-C and -R, expressed in developing and lesioned neural tissue, 7:2977-2981). In fact, for some cell types, specific ECM molecules, such as laminin or fibronectin, of ECM proteins, including fibronectin, collagen, and tenascin (Pearson, C.A. et al. (1988) EMBO J. can be stimulated by growth factors. For example, TGF-\beta stimulates fibroblasts to produce a variety linking the cytoskeleton with the extracellular matrix (ECM). The expression of ECM components division as well. This anchorage dependence may be associated with the formation of focal contacts dependent inhibition of cell division. Cells often demonstrate an anchorage dependence of cell quantities in a perfused system will grow to even higher cell densities before reaching density-

Cancers and immune disorders are characterized by uncoordinated cell proliferation. Cancers

proteins involved in cell cycle regulation (Nigg, E.A. (1995) BioEssays 17:471-480). treatment strategy involves reestablishing control over cell cycle progression by manipulation of the 30 changes in the protein complexes that normally control progression through the cell cycle. A primary oncogenes include v-src, v-abl, and v-fps. Certain cell proliferation disorders can be identified by integrated into the human genome after infection of human cells by certain viruses. Examples of viral transducers, nuclear transcription factors, and cell-cycle control proteins. Viral oncogenes are cell cycle controls. These classes include growth factors, growth factor receptors, intracellular signal 52 altering transcriptional control of cell proliferation. Five classes of oncoproteins are known to affect respect to location or amount of expression. The latter category of oncoprotein causes cancer by are mutant isoforms of the normal protein, and other oncoproteins are abnormally expressed with oncogenes encode oncoproteins which convert normal cells into malignant cells. Some oncoproteins are associated with the activation of oncogenes which are derived from normal cellular genes. These 07

between chromosomes 9 and 22 that moves a truncated portion of the proto-oncogene c-abl to the leukemia and a subset of acute lymphoblastic leukemias, results from a reciprocal translocation chromosomal translocation. The Philadelphia chromosome, characteristic of chronic myeloid mdm2, Cip1, p16, and cyclin D. Transformation of normal genes to oncogenes may also occur by 2, mutated G<sub>5</sub>, src, abl, ras, crk, jun, fos, myc, and mutated tumor-suppressor genes such as RB, p53, Many oncogenes have been identified and characterized. These include sis, erbA, erbB, her-

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breakpoint cluster region (bcr) on chromosome 22.

Mutations which hyperactivate oncogenes result in cell proliferation. Stimulation of a cell by growth factors activates two sets of gene products, the early-response genes and the delayed-response genes. Early-response gene products include myc, fos, and jun, all of which encode gene regulatory proteins. These regulatory proteins lead to the transcriptional activation of a second set of genes, the delayed-response genes, which include the cell-cycle regulators Cdk and cyclins. For example, the gene by enhancing the activity of a cellular transcription factor. The oncogenic properties of the Tax protein include transformation of primary T-lymphocytes and fibroblasts through cooperation with the a GTP- binding protein, Ras. Recently investigators have shown that Tax interacts with several protein Discs-Large, is common to membrane proteins thought to be involved in clustering receptors in growth factor signal transduction pathways (Rousset, R. et al. (1998) Oncogene 16:643-654).

Tumor-suppressor genes are involved in regulating cell proliferation. Mutations which cause

reduced or loss of function in tumor-suppressor genes result in uncontrolled cell proliferation. For example, the retinoblastoma gene product (RB), in a non-phosphorylated state, binds several early-response genes and suppresses their transcription, thus blocking cell division. Phosphorylation of RB causes it to dissociate from the genes, releasing the suppression, and allowing cell division to proceed.

Other gene products involved in cell proliferation, differentiation, and apoptosis are yet to be discovered. One method currently being utilized to help identify such new molecules involves comparisons between quiescent and proliferative tissues. For example, a subtractive hybridization screen of human placental cytotrophoblast cells identified 20 genes whose expression levels rose due to EGF induction of cell proliferation. (Morrish, D.W. et al. (1996) Placenta 17:431-441). Another method involves identification of molecules produced in cells treated with anti-tumorigenic agents, such as dithiolethiones. Presumably, the protective action of these anti-tumorigenic agents, such as dithiolethiones. Presumably, the protective action of these anti-tumorigenic agents is associated with the induction of tumor suppressor gene products (Primiano, T. et al. (1996) Carcinogenesis 17:2297-2303).

In another example, the candidate tumor-suppressor gene ING1, that codes a nuclear protein, p33ING1, is involved in the negative regulation of cell proliferation. The action of p33ING1 is

dependent upon the activity of another tumor-suppressor gene, p53. p53 is a cellular stress-responsive gene requiring the activity of p33ING1 to effectively induce growth inhibition of cells. p33ING1 and p53 have been shown to physically associate through immunoprecipitation studies (Garkavtsev, I. et al. (1998) Nature 391:295-298).

**Apoptosis** 

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Apoptosis is the genetically controlled process by which unneeded or defective cells undergo programmed cell death. Selective elimination of cells is as important for morphogenesis and tissue

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remodeling as is cell proliferation and differentiation. Lack of apoptosis may result in hyperplasia and other disorders associated with increased cell proliferation. Apoptosis is also a critical component of the immune response. Immune cells such as cytotoxic T-cells and natural killer cells prevent the spread of disease by inducing apoptosis in tumor cells and virus-infected cells. In addition, immune cells that fail to distinguish self molecules from foreign molecules must be

eliminated by apoptosis to avoid an autoimmune response.

Apoptotic cells undergo distinct morphological changes. Hallmarks of apoptosis include cell

shrinkage, nuclear and cytoplasmic condensation, and alterations in plasma membrane topology.

Biochemically, apoptotic cells are characterized by increased intracellular calcium concentration,

fragmentation of chromosomal DNA, and expression of novel cell surface components.

The molecular mechanisms of apoptosis are highly conserved, and many of the key protein

regulators and effectors of apoptosis have been identified. Apoptosis generally proceeds in response to a signal which is transduced intracellularly and results in altered patterns of gene expression and protein activity. Signaling molecules such as hormones and cytokines are known both to stimulate and to inhibit apoptosis through interactions with cell surface receptors. Transcription factors also play an important role in the onset of apoptosis. A number of downstream effector molecules, particularly proteases such as the cysteine proteases called caspases, have been implicated in the

play an important role in the onset of apoptosis. A number of downstream effector molecules, particularly proteases such as the cysteine proteases called caspases, have been implicated in the degradation of cellular components and the proteolytic activation of other apoptotic effectors. Aging and Senescence

Studies of the aging process or senescence have shown a number of characteristic cellular and molecular changes (Fauci, A.S. et al. (1998) Harrison's Principles of Internal Medicine, McGraw-Hill, New York NY, p.37). These characteristics include increases in chromosome structural abnormalities, DNA cross-linking, incidence of single-stranded breaks in DNA, losses in DNA methylation, and degradation of telomete regions. In addition to these DNA changes, post-translational alterations of proteins increase including deamidation, oxidation, cross-linking, and nonenzymatic glycosylation. Still further molecular changes occur in the mitochondria of aging cells through deterioration of structure. These changes eventually contribute to decreased function in

every organ of the body.

The discovery of new cell cycle and proliferation proteins and the polynucleotides encoding

them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of immune, developmental, and cell signaling disorders, and cell proliferative disorders including cancer.

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#### SUMMARY OF THE INVENTION

The invention features purified polypeptides, cell cycle and proliferation proteins, referred to collectively as "CCYPR-5," "CCYPR-1," "CCYPR-1," "CCYPR-3," "CCYPR-1," "CCYPR-1



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"CCYPR-12," "CCYPR-13," "CCYPR-14," "CCYPR-15," "CCYPR-15," "CCYPR-17," "CCYPR-24,"

"CCYPR-19," "CCYPR-20," "CCYPR-21," "CCYPR-22," "CCYPR-23," "CCYPR-24,"

"CCYPR-35," "CCYPR-36," "CCYPR-37," "CCYPR-38," "CCYPR-39," "CCYPR-30," "CCYPR-31," "CCYPR-32," "CCYPR-36," "CC

an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-54. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:1-54. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:55-108.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter

invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-54.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising

sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54,

The invention also provides a method for producing a polypeptide comprising an amino acid

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c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID MO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID MO:1-54. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the

polypeptide, and b) recovering the polypeptide so expressed.

polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence.

The invention further provides an isolated polynucleotide comprising a polynucleotide

Additionally, the invention provides an isolated antibody which specifically binds to a

sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, b) a naturally occurring polynucleotide sequence having at least NO:55-108, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide compress at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a

sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of 3) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, b) a naturally occurring polynucleotide sequence having at least 20% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, c) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, the invention further provides a method for detecting a target polynucleotide in a sample,

said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, b) a naturally occurring polynucleotide sequence having at least

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70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RMA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and,

optionally, if present, the amount thereof.

The invention further provides a pharmaceutical composition comprising an effective amount

of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an animally occurring amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional CCYPR, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of 3BQ mocurring amino acid sequence selected from the group consisting of SEQ mocurring amino acid sequence having at least 90% sequence identity to an amino acid sequence baving at least 90% sequence identity to an amino acid sequence baving at least 90% sequence identity to an amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ mociles and a minonogenic acid sequence selected from the group consisting of SEQ mociles and an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ mociles and an immunogenic agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutical composition comprising an agonist compound identified by the method of treating a disease of condition associated with decreased expression of functional CCYPR, comprising administering to a condition associated with decreased expression of functional composition.

an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino

Additionally, the invention provides a method for screening a compound for effectiveness as

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in need of such treatment the pharmaceutical composition. condition associated with overexpression of functional CCYPR, comprising administering to a patient acceptable excipient. In another alternative, the invention provides a method of treating a disease or composition comprising an antagonist compound identified by the method and a pharmaceutically antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The acid sequence selected from the group consisting of SEQ ID NO: 1-54, and d) an immunogenic

combining the polypeptide with at least one test compound under suitable conditions, and b) acid sequence selected from the group consisting of SEQ ID NO: 1-54. The method comprises a) selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an

The invention further provides a method of screening for a compound that specifically binds

specifically binds to the polypeptide. detecting binding of the polypeptide to the test compound, thereby identifying a compound that

The invention further provides a method of screening for a compound that modulates the

compound that modulates the activity of the polypeptide. change in the activity of the polypeptide in the presence of the test compound is indicative of a 30 test compound with the activity of the polypeptide in the absence of the test compound, wherein a presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the method comprises a) combining the polypeptide with at least one test compound under conditions fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The 52 acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence an amino acid sequence selected from the group consisting of SEQ ID MO:1-54, b) a naturally activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) 50

exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered sequence selected from the group consisting of SEQ ID NO:55-108, the method comprising a) altering expression of a target polynucleotide, wherein said target polynucleotide comprises a

expression of the target polynucleotide.

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The invention further provides a method for screening a compound for effectiveness in

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The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound;

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID

Scoup consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID

NO:55-108, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity

NO:55-108, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, iii) a naturally occurring polynucleotide sequence having at least NO:55-108, iii) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, iii) a naturally occurring polynucleotide sequence having at least NO:55-108, iii) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, iii) a polynucleotide sequence selected from the group complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of the above polynucleotide sequence; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated

## BRIEF DESCRIPTION OF THE TABLES

biological sample with the amount of hybridization complex in the treated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID MOs), clone identification numbers (clone IDs), cDMA libraries, and cDMA fragments used to assemble full-length sequences encoding CCYPR.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of CCYPR.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific

expression patterns of each nucleic acid sequence as determined by northern analysis; diseases,

disorders, or conditions associated with these tissues; and the vector into which each cDNA was

cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones

encoding CCYPR were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold

parameters.

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indicative of toxicity of the test compound.

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## DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Unless defined otherwise, all technical and scientific terms used herein have the same

## DEFINITIONS

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"CCYPR" refers to the amino acid sequences of substantially purified CCYPR obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of CCYPR. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of CCYPR either by directly interacting with CCYPR or by acting on components of the biological pathway in which CCYPR participates.

An "allelic variant" is an alternative form of the gene encoding CCYPR. Allelic variants may

result from at least one mutation in the nucleic acid sequence and may result in altered mRMAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding CCYPR include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as CCYPR or

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The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, ςī isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged residues, as long as the biological or immunological activity of CCYPR is retained. For example, polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the equivalent CCYPR. Deliberate amino acid substitutions may be made on the basis of similarity in or substitutions of amino acid residues which produce a silent change and result in a functionally encoding CCYPR. The encoded protein may also be "altered," and may contain deletions, insertions, variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence probe of the polynucleotide encoding CCYPR, and improper or unexpected hybridization to allelic are polymorphisms which may or may not be readily detectable using a particular oligonucleotide a polypeptide with at least one functional characteristic of CCYPR. Included within this definition

polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence associated with the recited protein molecule. "Amplification" relates to the production of additional copies of a nucleic acid sequence.

Amplification is generally carried out using polymerase chain reaction (PCR) technologies well

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of CCYPR. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of CCYPR either by directly interacting with CCYPR or by acting on components of the biological pathway in which CCYPR participates.

Antibodies that bind CCYPR polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RMA, or synthesized chemically, and can be conjugated to a carrier protein if desired.

Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')2, and Fv fragments, which are capable of binding an epitopic determinant.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that

the animal.

known in the art.

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makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5'-methyl cytosine, 2'-deoxyuracil, or 7'-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or nucleic acid sequence produced by the cell to form duplexes which block either transcription or designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical protein laving structural, regulatory, or biochemical protein laving structural, regulatory, or biochemical

functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic CCYPR, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

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antibodies.

a given amino acid sequence. The composition may composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding CCYPR or fragments of CCYPR may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl deployed in an aqueous solution containing salts (e.g., Denhard's solution, dry milk, salmon sperm DNA, etc.). "Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated "Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated "Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated

A "composition comprising a given polynucleotide sequence" and a "composition comprising

DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap

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University of Washington, Seattle WA). Some sequences have been both extended and assembled to

interfere with the properties of the original protein, i.e., the structure and especially the function of "Conservative amino acid substitutions" are those substitutions that are predicted to least

amino acids which may be substituted for an original amino acid in a protein and which are regarded the protein is conserved and not significantly changed by such substitutions. The table below shows

	lsV.	Ile, Leu, Thr
	ıγT	His, Phe, Trp
57	${f q}_1{f T}$	Туг Туг
	тhт	Ser, Val
	Ser	Суз, Тћг
	Ъре	His, Met, Leu, Trp, Tyr
	лэМ	Leu, Ile
20	Γλε	Arg, Gln, Glu
	Гeп	lle, Val
	əII	Leu, Val
	siH	Asn, Arg, Gln, Glu
	Gly	ßlA
SI	olb	Asp, Gln, His
	Gln	Asn, Glu, His
	Cys	Ala, Ser
	qsA	Asn, Glu
	nzA	Asp, Gln, His
10	gıA	His, Lys
	ьlA	GJy, Ser
	Original Residue	Conservative Substitution

as conservative amino acid substitutions.

produce the consensus sequence.

(b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, 30 Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the the side chain.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. 32 absence of one or more amino acid residues or nucleotides.

retains at least one biological or immunological function of the polypeptide from which it was A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that polypeptide which retains at least one biological or immunological function of the natural molecule. hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a Chemical modifications of a polynucleotide sequence can include, for example, replacement of

derived.

measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide. A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a

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A "fragment" is a unique portion of CCYPR or the polynucleotide encoding CCYPR which is

identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residues. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For testidues in length. Fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:55-108, for example, as distinct from any other sequence in that specifically identifies SEQ ID NO:55-108, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:55-108 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:55-108 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:55-108 and the region of SEQ ID NO:55-108 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-54 is encoded by a fragment of SEQ ID NO:55-108. A

fragment of SEQ ID NO:1-54 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-54. For example, a fragment of SEQ ID NO:1-54 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-54. The precise length of a fragment of SEQ ID NO:1-54 and the region of SEQ ID NO:1-54 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the

intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation

codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.
"Homology" refers to sequence similarity or, interchangeably, sequence identity, between

two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

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Percent identity between polynucleotide sequences may be determined using the default

parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent

Alternatively, a suite of commonly used and freely available sequence comparison algorithms

is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at analysis programs including "blastn," that is used to align a known polynucleotide sequence trom a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html.

The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST 2 programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for mismatch: -2

25 Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

similarity" between aligned polynucleotide sequences.

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Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length nucleotides. Such lengths are exemplary only, and it is understood that any fragment length describe a length over which percentage identity may be measured.

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Mucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to

the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default

parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise alignments of the MCBI BLAST software suite may be used. For example, for a pairwise

comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for

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Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for instance, a fragment of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for chromosome replication, segregation and maintenance.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain

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The term "humanized antibody" refers to an antibody molecule in which the amino acid

sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a

complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about

under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T<sub>m</sub>) for the specific sequence at a defined ionic strength and pH. The T<sub>m</sub> is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T<sub>m</sub> and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature

High stringency conditions for hybridization between polynucleotides of the present

invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides. The term "hybridization complex" refers to a complex formed between two nucleic acid

sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., Cot or Rot analysis) or formed between one

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nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate

The words "insertion" and "addition" refer to changes in an amino acid or nucleotides, respectively.

to which cells or their nucleic acids have been fixed).

disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

"Immune response" can refer to conditions associated with inflammation, trauma, immune

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of CCYPR which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of CCYPR which is useful in any of the antibody production methods disclosed herein or known in

of CC 1 PK which is useful in any of the anthousy production methods disclosed herein of known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides,

polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other

chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of CCYPR. For example, modulation

20 may cause an increase or a decrease in protein activity, binding characteristics, or any other

biological, functional, or immunological properties of CCYPR.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide,

polynucleotide, or any fragment thereof. These phrases also refer to DMA or RMA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PMA), or to any DMA-like or RMA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a

functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PMA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PMAs preferentially bind complementary single stranded DMA or RMA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification, of an CCYPR may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in

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the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of CCYPR.

"Probe" refers to nucleic acid sequences encoding CCYPR, their complements, or fragments

thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target

identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for

example Sambrook, J. et al., 1989, <u>Molecular Cloning: A Laboratory Manual</u>, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al., 1987, <u>Current Protocols in Molecular Biology</u>, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al., 1990, <u>PCR Primer Pairs</u> can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such

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purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larget polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific programs may also be obtained from their respective sources and modified to meet the user's specific

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oligonucleotide selection are not limited to those described above. identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to polynucleotide fragments identified by any of the above selection methods are useful in hybridization unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both thereby allowing selection of primers that hybridize to either the most conserved or least conserved Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping

sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques This artificial combination is often accomplished by chemical synthesis or, more commonly, by the that is made by an artificial combination of two or more otherwise separated segments of sequence. A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence

vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a

expressed, inducing a protective immunological response in the mammal.

(UTRs). Regulatory elements interact with host or viral proteins which control transcription, regions of a gene and includes enhancers, promoters, introns, and 3' and 3' untranslated regions A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated

other moieties known in the art. chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, "Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid,

instead of deoxyribose. nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the An "RMA equivalent," in reference to a DMA sequence, is composed of the same linear

RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc. extract from a cell; chromosome, organelle, or membrane isolated from a cell; a cell; genomic DMA, acids encoding CCYPR, or fragments thereof, or CCYPR itself, may comprise a bodily fluid; an The term "sample" is used in its broadest sense. A sample suspected of containing nucleic

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translation, or RNA stability.

transform a cell.

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The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular atructure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which

The term "substantially purified" refers to nucleic acid or amino acid sequences that are

they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides

by different amino acid residues or nucleotides, respectively. "Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters,

chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polymucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell

type or tissue under given conditions at a given time. "Transformation" describes a process by which exogenous DNA is introduced into a recipient

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cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transfering transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to

animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria,

cyanobacteria, fungi, plants, and animals. The isolated DMA of the present invention can be

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introduced into the host by methods known in the art, for example infection, transfection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989),

50 presence of SNPs may be indicative of, for example, a certain population, a disease state, or a polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The between individuals of a given species. Polymorphic variants also may encompass "single nucleotide each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene another. The resulting polypeptides generally will have significant amino acid identity relative to reference molecule. Species variants are polynucleotide sequences that vary from one species to polypeptide may possess additional functional domains or lack domains that are present in the polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding have significant identity to a reference molecule, but will generally have a greater or lesser number of an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may 10 greater sequence identity over a certain defined length. A variant may be described as, for example, least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or 1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having ς

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at

least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

The invention is based on the discovery of new human cell cycle and proliferation proteins (CCYPR), the polynucleotides encoding CCYPR, and the use of these compositions for the diagnosis, treatment, or prevention of immune, developmental, and cell signaling disorders, and cell

CCYPR. Columns 1 and 2 show the sequence identification numbers (SEQ ID MOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each CCYPR were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding

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proliferative disorders including cancer.

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propensity for a disease state.

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corresponding cDUA libraries. Clones for which cDUA libraries are not indicated were derived from

pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5.

The Incyte clones and GenBank cDNA sequences, where indicated, in column 5 were used to

assemble the consensus nucleotide sequence of each CCYPR and are useful as fragments in

hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention:

column 1 references the SEQ ID MO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis along with relevant citations, all of which are expressly incorporated by reference herein in their entirety; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

associated with nucleotide sequences encoding CCYPR. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:55-108 and to distinguish between SEQ ID NO:55-108 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express CCYPR as a fraction of total tissues expressing CCYPR. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing CCYPR as a fraction of total tissues expressing

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding CCYPR were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2. SEQ ID NO:61 maps to chromosome 5 within the interval from 141.40 to 142.60

each cDNA library. Of particular note is the expression of SEQ ID NO:66 in inflammatory tissues. It

should be noted that SEQ ID MO:76 was found to be expressed predominantly in nervous tissue.

centiMorgans. This interval also contains gene(s) and/or EST(s) associated with corneal dystrophy and deafness.

SEQ ID MO:73 maps to chromosome 2 within the interval from 73.80 to 83.50 centiMorgans. This interval also contains gene(s) and/or EST(s) associated with hereditary nonpolyposis colorectal carcinoma and Muir-Torre syndrome. SEQ ID MO:74 maps to chromosome 19 within the interval from 41.70 to 58.70 centiMorgans. SEQ ID MO:75 maps to chromosome 17 within the interval from

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The interval on chromosome X from 112.80 to 139.40 centiMorgans also contains gene(s) and/or 160.00 centiMorgans, and to chromosome X within the interval from 112.80 to 139.40 centiMorgans. interval from 143.30 to 153.90 centiMorgans, to chromosome 3 within the interval from 156.20 to human breast cancer (BRCA1) gene region. SEQ ID NO:76 maps to chromosome 1 within the 62.90 to 64.20 centiMorgans. This interval also contains gene(s) and/or EST(s) located within the

SEQ ID NO:77 maps to chromosome 23 within the interval from 173.60 to 179.80 EST(s) associated with X-linked agammaglobulinaemia.

81.20 centiMorgans. to 42.70 centiMorgans. SEQ ID NO:105 maps to chromosome 19 within the interval from 69.90 to centiMorgans to q-terminus. SEQ ID NO:104 maps to chromosome 18 within the interval from 32.40 interval from 95.50 to 103.70 centiMorgans, and to chromosome 6 within the interval from 158.50 interval from 40.30 to 60.00 centiMorgans. SEQ ID MO:100 maps to chromosome 14 within the interval from 22.40 to 40.70 centiMorgans. SEQ ID MO:98 maps to chromosome 8 within the the interval from 124.20 to 126.50 centiMorgans. SEQ ID NO:91 maps to chromosome 2 within the chromosome 3 within the interval from 16.50 to 43.00 centiMorgans, and to chromosome 6 within SEQ ID NO:90 maps to chromosome 2 within the interval from 236.10 to 240.20 centiMorgans, to SEQ ID NO:81 maps to chromosome 7 within the interval from 167.60 centiMorgans to q-terminus. SEQ ID NO:78 maps to chromosome 3 within the interval from 200.00 to 213.70 centiMorgans. centiMorgans, and to chromosome 11 within the interval from 136.90 centiMorgans to q-terminus.

structural characteristic of CCYPR. sequence identity to the CCYPR amino acid sequence, and which contains at least one functional or has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid The invention also encompasses CCYPR variants. A preferred CCYPR variant is one which

sugar backbone is composed of ribose instead of deoxyribose. sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sequences of SEQ ID NO:55-108, as presented in the Sequence Listing, embrace the equivalent RNA from the group consisting of SEQ ID NO:55-108, which encodes CCYPR. The polynucleotide embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected

The invention also encompasses polynucleotides which encode CCYPR. In a particular

The invention also encompasses a variant of a polynucleotide sequence encoding CCYPR. In

95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting NO:55-108 which has at least about 70%, or alternatively at least about 85%, or even at least about polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID sequence encoding CCYPR. A particular aspect of the invention encompasses a variant of a least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at

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of SEQ ID NO:55-108. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of CCYPR.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the

genetic code, a multitude of polynucleotide sequences encoding CCYPR, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring CCYPR, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode CCYPR and its variants are generally capable

of hybridizing to the nucleotide sequence of the naturally occurring CCYPR under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding CCYPR or its derivatives possessing a substantially different codon usage, e.g., inclusion of nonpeptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding CCYPR and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode CCYPR and CCYPR derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding CCYPR or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of

hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:55-108 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol.

"Definitions."

Methods for DMA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DMA polymerase I, SEQUEMASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway MI), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably,

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sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno MV), PTC200 thermal cyclet (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cyclet (PE Biosystems). Sequencing is then carried out using either the system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., analyzed using a variety of algorithms which are well known in the art. (See, e.g., busubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit

7.7; Meyers, R.A. (1995) Molecular Biology and Biolechnology, Wiley VCH, New York MY, pp.

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30 about 68°C to 72°C. length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of Biosciences, Plymouth MM) or another appropriate program, to be about 22 to 30 nucleotides in using commercially available software, such as OLIGO 4.06 Primer Analysis software (National and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries 52 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. of unknown sequence before performing PCR. Other methods which may be used to retrieve digestions and ligations may be used to insert an engineered double-stranded sequence into a region 70 M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids sequence from a circularized template. The template is derived from restriction fragments comprising Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown ςī DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic such as promoters and regulatory elements. For example, one method which may be employed, sequence and employing various PCR-based methods known in the art to detect upstream sequences, 10 The nucleic acid sequences encoding CCYPR may be extended utilizing a partial nucleotide

When screening for full-length cDMAs, it is preferable to use libraries that have been size-selected to include larger cDMAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDMA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary

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sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode CCYPR may be cloned in recombinant DNA molecules that direct expression of degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express CCYPR.

not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotidemant may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such

known in the art in order to alter CCYPR-encoding sequences for a variety of purposes including, but

The nucleotide sequences of the present invention can be engineered using methods generally

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32 mannet. maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable homologous genes in the same gene family, either from the same or different species, thereby optimized. Alternatively, fragments of a given gene may be recombined with fragments of point mutations may be recombined, screened, and then reshuffled until the desired properties are breeding and rapid molecular evolution. For example, fragments of a single gene containing random 30 DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" properties. These preferred variants may then be pooled and further subjected to recursive rounds of subjected to selection or screening procedures that identify those gene variants with the desired variants is produced using PCR-mediated recombination of gene fragments. The library is then to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene 52 improve the biological properties of CCYPR, such as its biological or enzymatic activity or its ability Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number

In another embodiment, sequences encoding CCYPR may be synthesized, in whole or in part,

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using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Mucleic Acids Symp. Ser. 7:225-232.)

Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Mucleic Acids Symp. Ser. 7:225-232.)

Alternatively, CCYPR itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York MY, pp. 55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequence of CCYPR, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.)

The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, <u>supra</u>, pp. 28-53.)

In order to express a biologically active CCYPR, the nucleotide sequences encoding CCYPR

The peptide may be substantially purified by preparative high performance liquid

Methods which are well known to those skilled in the art may be used to construct expression (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.) 30 may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. initiation codons may be of various origins, both natural and synthetic. The efficiency of expression frame ATG initiation codon should be provided by the vector. Exogenous translational elements and sequence, or a fragment thereof, is inserted, exogenous translational control signals including an intranscriptional or translational control signals may be needed. However, in cases where only coding 52 upstream regulatory sequences are inserted into the appropriate expression vector, no additional e.g. the Kozak sequence. In cases where sequences encoding CCYPR and its initiation codon and sequences encoding CCYPR. Such signals include the ATG initiation codon and adjacent sequences, specificity. Specific initiation signals may also be used to achieve more efficient translation of polynucleotide sequences encoding CCYPR. Such elements may vary in their strength and constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in sequence in a suitable host. These elements include regulatory sequences, such as enhancers, contains the necessary elements for transcriptional and translational control of the inserted coding or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which

vectors containing sequences encoding CCYPR and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning. A sand in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning. A sand in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning. A sand in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1995) Molecular Cloning. A sand in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1995) Molecular Cloning. A sand in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1995) Molecular Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and

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A variety of expression vector/host systems may be utilized to contain and express sequences

The invention is not limited by the host cell employed. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. Micola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al., (1993) Proc. Matl. Acad. Sci. delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, SI NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 1945; Takamatsu, N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-Enzymol. 153:516-544; Scorer, C.A. et al. (1994) Bio/Technology 12:181-184; Engelhard, E.K. et al. G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, <u>supra;</u> Ausubel, <u>supra;</u> Van Heeke, mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower transformed with yeast expression vectors; insect cell systems infected with viral expression vectors transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast encoding CCYPR. These include, but are not limited to, microorganisms such as bacteria

In bacterial systems, a number of cloning and expression vectors may be selected depending, upon the use intended for polynucleotide sequences encoding CCYPR. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding CCYPR can be achieved using a

multifunctional <u>E. coli</u> vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORTI plasmid (Life Technologies). Ligation of sequences encoding CCYPR into the vector's multiple cloning site disrupts the lacZ gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequencing, single strand rescue with helper phage, and creation of Chem. 264:5503-5509.) When large quantities of CCYPR are needed, e.g. for the production of containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of CCYPR. A number of vectors be used expression systems may be used for production of CCYPR. A number of vectors

containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast <u>Saccharomyces cerevisiae</u> or <u>Pichia pastoris</u>. In addition, such

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vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, supra; and Scorer, supra.)

Plant systems may also be used for expression of CCYPR. Transcription of sequences

encoding CCYPR may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding CCYPR may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses CCYPR in host cells. (See, e.g., Logan, I. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Mat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of CCYPR in cell lines is preferred. For example, sequences encoding CCYPR can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These

include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in tk and apr cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic,

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or herbicide resistance can be used as the basis for selection. For example, dhy confers resistance to methotrexate; neo confers resistance to the aminoglycosides neomycin and G-418; and als and par confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Matl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Matl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate B-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding CCYPR is inserted within a marker gene sequence, transformed cells containing a marker gene can be placed in tandem with a sequence encoding CCYPR under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

express CCYPR may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of CCYPR using either

In general, host cells that contain the nucleic acid sequence encoding CCYPR and that

specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on CCYPR is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding CCYPR include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide.

A wide variety of labels and conjugation techniques are known by those skilled in the art and

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Host cells transformed with nucleotide sequences encoding CCYPR may be cultured under agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like. ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety and may be used to synthesize RMA probes in vitro by addition of an appropriate RMA polymerase for the production of an mRNA probe. Such vectors are known in the art, are commercially available, Alternatively, the sequences encoding CCYPR, or any fragments thereof, may be cloned into a vector

In addition, a host cell strain may be chosen for its ability to modulate expression of the direct secretion of CCYPR through a prokaryotic or eukaryotic cell membrane. containing polynucleotides which encode CCYPR may be designed to contain signal sequences which and/or the vector used. As will be understood by those of skill in the art, expression vectors produced by a transformed cell may be secreted or retained intracellularly depending on the sequence conditions suitable for the expression and recovery of the protein from cell culture. The protein

modification and processing of the foreign protein. American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the Different host cells which have specific cellular machinery and characteristic mechanisms for "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, inserted sequences or to process the expressed protein in the desired fashion. Such modifications of

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In another embodiment of the invention, natural, modified, or recombinant nucleic acid

proteolytic cleavage site located between the CCYPR encoding sequence and the heterologous that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a purification of fusion proteins using commercially available monoclonal and polyclonal antibodies 32 metal-chelate resins, respectively. FLAG, c-myc, and hemagglutinin (HA) enable immunoaffinity cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and c-myc, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), 30 and peptide moieties may also facilitate purification of fusion proteins using commercially available facilitate the screening of peptide libraries for inhibitors of CCYPR activity. Heterologous protein containing a heterologous moiety that can be recognized by a commercially available antibody may fusion protein in any of the aforementioned host systems. For example, a chimeric CCYPR protein sequences encoding CCYPR may be ligated to a heterologous sequence resulting in translation of a 52

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supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, protein sequence, so that CCYPR may be cleaved away from the heterologous moiety following

precursor, for example, 35S-methionine. T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid systems couple transcription and translation of protein-coding sequences operably associated with the in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These In a further embodiment of the invention, synthesis of radiolabeled CCYPR may be achieved

screened for specific binding to CCYPR. Examples of test compounds include antibodies, that specifically bind to CCYPR. At least one and up to a plurality of test compounds may be CCYPR of the present invention or fragments thereof may be used to screen for compounds

oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of

contacted with a test compound and binding, stimulation, or inhibition of activity of either CCYPR or E. coli. Cells expressing CCYPR or cell membrane fractions which contain CCYPR are then protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or these compounds involves producing appropriate cells which express CCYPR, either as a secreted compound can be rationally designed using known techniques. In one embodiment, screening for binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which CCYPR natural binding partner. (See, Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): CCYPR, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a

solid support. libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical 30 Altematively, the assay may detect or measure binding of a test compound in the presence of a. solution or affixed to a solid support, and detecting the binding of CCYPR to the compound. the assay may comprise the steps of combining at least one test compound with CCYPR, either in detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example,

An assay may simply test binding of a test compound to the polypeptide, wherein binding is

CCYPR activity, wherein CCYPR is combined with at least one test compound, and the activity of or inverse agonists. In one embodiment, an assay is performed under conditions permissive for that modulate the activity of CCYPR. Such compounds may include agonists, antagonists, or partial CCYPR of the present invention or fragments thereof may be used to screen for compounds

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the compound is analyzed.

purification of fusion proteins.

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CCYPR in the presence of a test compound is compared with the activity of CCYPR in the absence of the test compound. A change in the activity of CCYPR in the presence of the test compound is indicative of a compound that modulates the activity of CCYPR. Alternatively, a test compound is combined with an in vitro or cell-free system comprising CCYPR under conditions suitable for modulates the activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of CCYPR may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding CCYPR or their mammalian homologs

therapeutic or toxic agents. heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce 50 blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific genome by homologous recombination. Alternatively, homologous recombination takes place using M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, embryo and grown in culture. The ES cells are transformed with a vector containing the gene of example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For 0I stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal may be "knocked out" in an animal model system using homologous recombination in embryonic

Polynucleotides encoding CCYPR may also be manipulated <u>in vitro</u> in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

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Polynucleotides encoding CCYPR can also be used to create "knockin" humanized animals

130 (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding CCYPR is injected into animal ES cells, and the injected into blastulae, and the injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease.

35 Alternatively, a mammal inbred to overexpress CCYPR, e.g., by secreting CCYPR in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-

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Chemical and structural similarity, e.g., in the context of sequences and motifs, exists

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## **THERAPEUTICS**

between regions of CCYPR and cell cycle and proliferation proteins. In addition, the expression of CCYPR is closely associated with inflammation, trauma, cell proliferation and cancer. Therefore, CCYPR appears to play a role in immune, developmental, and cell signaling disorders, and cell proliferative disorders including cancer. In the treatment of disorders associated with increased CCYPR expression or activity of CCYPR. In the treatment of disorders associated with decreased to decrease the expression or activity of CCYPR. In the increase the expression or activity of CCYPR.

Therefore, in one embodiment, CCYPR or a fragment or derivative thereof may be

sensorineural hearing loss, and disorders of immune cell activation; a cell signaling disorder and cerebral palsy, spina bifida, anencephaly, craniorachisis, congenital glaucoma, cataract, neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, 30 lymphoma, leukemia, and myeloma; a developmental disorder such as renal tubular acidosis, anemia, fungal, parasitic, protozoal, and helminthic infections, trauma, and hematopoietic cancer including syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic 52 pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, irritable bowel syndrome, mixed connective tissue disorder (MCTD), multiple sclerosis, myasthenia disease, Hashimoto's thyroiditis, paroxysmal noctumal hemoglobinuria, hepatitis, hypereosinophilia, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' 50 diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, bursitis, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (ADS), Addison's activity of CCYPR. Examples of such disorders include, but are not limited to, an immune disorder administered to a subject to treat or prevent a disorder associated with decreased expression or

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expression or activity of CCYPR including, but not limited to, those described above. thereof may be administered to a subject to treat or prevent a disorder associated with decreased In another embodiment, a vector capable of expressing CCYPR or a fragment or derivative uterus. pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thyroid, and breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, paroxysmal noctumal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, gynecomastia; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign associated with absence of androgen receptors, syndrome of  $\delta$   $\alpha$ -reductase, a disruption of germinal cell aplasia, hypergonadal disorders associated with Leydig cell tumors, androgen resistance post-menopausal women, osteoporosis; and, in men, Leydig cell deficiency, male climacteric phase, hermaphroditism, hirsutism and virilization, breast cancer, and fibrocystic breast disease; and, in teratogenesis, hyperprolactinemia, isolated gonadotropin deficiency, amenorrhea, galactorrhea, an endometrial or ovarian tumor, a uterine fibroid, autoimmune disorders, an ectopic pregnancy, perturbations of the menstrual cycle, polycystic ovarian disease, ovarian hyperstimulation syndrome, prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, with alkalosis; disorders associated with gonadal steroid hormones such as: in women, abnormal adrenals such as hyperplasia, carcinoma, or adenoma of the adrenal cortex, hypertension associated as Type I or Type II diabetes mellitus and associated complications; disorders associated with the with hyperparathyroidism including Conn disease (chronic hypercalemia); pancreatic disorders such including goiter, myxedema, acute thyroiditis associated with bacterial infection; disorders associated secretion (SIADH) often caused by benign adenoma; disorders associated with hypothyroidism including acromegaly, giantism, and syndrome of inappropriate antidiuretic hormone (ADH) disorders, and complications due to head trauma; disorders associated with hyperpituitarism hypophysectomy, aneurysms, vascular malformations, thrombosis, infections, immunological lesions such as primary brain tumors, adenomas, infarction associated with pregnancy, including endocrine disorders such as disorders of the hypothalamus and pituitary resulting from

treat or prevent a disorder associated with decreased expression or activity of CCYPR including, but

In a further embodiment, a pharmaceutical composition comprising a substantially purified

CCYPR in conjunction with a suitable pharmaceutical carrier may be administered to a subject to

not limited to, those provided above.

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In still another embodiment, an agonist which modulates the activity of CCYPR may be

administered to a subject to treat or prevent a disorder associated with decreased expression or

activity of CCYPR including, but not limited to, those listed above.

In a further embodiment, an antagonist of CCYPR may be administered to a subject to treat or

prevent a disorder associated with increased expression or activity of CCYPR. Examples of such disorders include, but are not limited to, those immune, developmental, and cell signaling disorders, and cell proliferative disorders including cancer, described above. In one aspect, an antibody which specifically binds CCYPR may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express CCYPR.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding CCYPR may be administered to a subject to treat or prevent a disorder associated with

encoding CCYPR may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of CCYPR including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary

sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of CCYPR may be produced using methods which are generally known in the

art. In particular, purified CCYPR may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind CCYPR. Antibodies to CCYPR may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimet formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with CCYPR or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral

increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to

CCYPR have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches

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Of CCYPR amino acids may be fused with those of another protein, such as KLH, and antibodies to

the chimeric molecule may be produced.

the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J.

Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the

Monoclonal antibodies to CCYPR may be prepared using any technique which provides for

splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce CCYPR-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g.,

Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)
Antibodies may also be produced by inducing in vivo production in the lymphocyte

population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for CCYPR may also be generated.

For example, such fragments include, but are not limited to, F(ab')<sub>2</sub> fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D.

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoassays using either immunoassays typically involve the measurement of complex formation between CCYPR and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies may also be employed (Pound, supra).

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et al. (1989) Science 246:1275-1281.)

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for CCYPR. Affinity is expressed as an association constant, K<sub>a</sub>, which is defined as the molar concentration of CCYPR-antibody complex

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which the CCYPR-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K<sub>a</sub> ranging from about 109 to 1012 L/mole are preferred for use in immunoassays in for a particular CCYPR epitope, represents a true measure of affinity. High-affinity antibody for CCYPR. The K<sub>a</sub> determined for a preparation of monoclonal antibodies, which are monospecific affinities for multiple CCYPR epitopes, represents the average affinity, or avidity, of the antibodies The K<sub>n</sub> determined for a preparation of polyclonal antibodies, which are heterogeneous in their divided by the molar concentrations of free antigen and free antibody under equilibrium conditions.

Monoclonal Antibodies, John Wiley & Sons, New York NY). Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical immunopurification and similar procedures which ultimately require dissociation of CCYPR, preparations with K<sub>a</sub> ranging from about 106 to 107 L/mole are preferred for use in

Catty, <u>supra</u>, and Coligan et al., <u>supra</u>.) guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., of CCYPR-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, determine the quality and suitability of such preparations for certain downstream applications. For

The titer and avidity of polyclonal antibody preparations may be further evaluated to

(.IV swatoT encoding CCYPR. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., fragments can be designed from various locations along the coding or control regions of sequences encoding CCYPR. Such technology is well known in the art, and antisense oligonucleotides or larger (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene of gene expression can be achieved by designing complementary sequences or antisense molecules fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications In another embodiment of the invention, the polynucleotides encoding CCYPR, or any

gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral Slater, J.E. et al. (1998) J. Allergy Clin. Immunol. 102(3):469-475; and Scanlon, K.J. et al. (1995) complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence sequences into appropriate target cells can be used. Antisense sequences can be delivered In therapeutic use, any gene delivery system suitable for introduction of the antisense

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systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Mucleic Acids Res. 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding CCYPR may be used for

CCYPR from an appropriate population of transduced cells may alleviate the clinical manifestations case where a genetic deficiency in CCYPR expression or regulation causes disease, the expression of 50 brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Matl. Acad. Sci. USA. 93:11395-11399), (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. cell proliferation), or (iii) express a protein which affords protection against intracellular parasites express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated R.G. (1995) Science 270:404-410; Verma, I.M. and Somia, N. (1997) Nature 389:239-242)), (ii) hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene. (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by Xsomatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency

In a further embodiment of the invention, diseases or disorders caused by deficiencies in CCYPR are treated by constructing mammalian expression vectors encoding CCYPR and introducing these vectors by mechanical means into CCYPR-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii)

use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

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caused by the genetic deficiency.

Expression vectors that may be effective for the expression of CCYPR include, but are not

limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). CCYPR may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β-actin genes), (ii) an inducible promoter (e.g., the

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gene encoding CCYPR from a normal individual. and H.M. Blau, supra), or (iii) a tissue-specific promoter or the native promoter of the endogenous FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA

these standardized mammalian transfection protocols. (1982) EMBO J. 1:841-845). The introduction of DMA to primary cells requires modification of (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. parameters. In the alternative, transformation is performed using the calcium phosphate method polynucleotides to target cells in culture and require minimal effort to optimize experimental TRANSFECTION KIT, available from invitrogen) allow one with ordinary skill in the art to deliver Commercially available liposome transformation kits (e.g., the PERFECT LIPID

polynucleotide encoding CCYPR under the control of an independent promoter or the retrovirus long

In another embodiment of the invention, diseases or disorders caused by genetic defects with

respect to CCYPR expression are treated by constructing a retrovirus vector consisting of (i) the

7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020cells), and the return of transduced cells to a patient are procedures well known to persons skilled in reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4\* Tdiscloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and 52 receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for Natl. Acad. Sci. USA 92:6733-6737), incorporated by reference herein. The vector is propagated in commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are element (RRE) along with additional retrovirus cis-acting RNA sequences and coding sequences terminal repeat (LTR) promoter, (ii) appropriate RMA packaging signals, and (iii) a Rev-responsive

polynucleotides encoding CCYPR to cells which have one or more genetic abnormalities with respect In the alternative, an adenovirus-based gene therapy delivery system is used to deliver

Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. USA 95:1201-1206; Su, L. (1997) Blood 89:2283-

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incorporated by reference herein. Annu. Rev. Nutr. 19:511-544; and Verma, I.M. and N. Somia (1997) Nature 18:389:239-242, both hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) described in U.S. Patent Mumber 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to to the expression of CCYPR. The construction and packaging of adenovirus-based vectors are well

In another alternative, a herpes-based, gene therapy delivery system is used to deliver

ordinary skill in the art. of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of plasmids containing different segments of the large herpesvirus genomes, the growth and propagation 52 herpesvirus sequences, the generation of recombinant virus following the transfection of multiple (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. taught by this patent are the construction and use of recombinant HSV strains deleted for ICP27 cell under the control of the appropriate promoter for purposes including human gene therapy. Also HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is Res. 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has a tropism. The construction and packaging of herpes-based vectors are well known to those with especially valuable for introducing CCYPR to cells of the central nervous system, for which HSV has respect to the expression of CCYPR. The use of herpes simplex virus (HSV)-based vectors may be polynucleotides encoding CCYPR to target cells which have one or more genetic abnormalities with

CCYPR-coding RNAs and the synthesis of high levels of CCYPR in vector transduced cells. While alphavirus genome in place of the capsid-coding region results in the production of a large number of (e.g., protease and polymerase). Similarly, inserting the coding sequence for CCYPR into the 32 resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, alphavirus RWA replication, a subgenomic RWA is generated that normally encodes the viral capsid on the SFV genome (Garoff, H. and K.-l. Li (1998) Curr. Opin. Biotech. 9:464-469). During Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based

deliver polynucleotides encoding CCYPR to target cells. The biology of the prototypic alphavirus,

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to

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manipulating infectious cDMA clones of alphaviruses, performing alphavirus cDMA and RMA cells in a population may require the sorting of cells prior to transduction. The methods of allow the introduction of CCYPR into a variety of cell types. The specific transduction of a subset of application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIM) alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a

transfections, and performing alphavirus infections, are well known to those with ordinary skill in the

Oligonucleotides derived from the transcription initiation site, e.g., between about positions

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177.) A complementary sequence or antisense molecule may also be designed to block translation of and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using because it causes inhibition of the ability of the double helix to open sufficiently for the binding of inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly,

RAA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of mRNA by preventing the transcript from binding to ribosomes.

endonucleolytic cleavage of sequences encoding CCYPR. engineered hammerhead molif ribozyme molecules may specifically and efficiently catalyze molecule to complementary target RMA, followed by endonucleolytic cleavage. For example,

Specific ribozyme cleavage sites within any potential RNA target are initially identified by

oligonucleotides using ribonuclease protection assays. candidate targets may also be evaluated by testing accessibility to hybridization with complementary secondary structural features which may render the oligonucleotide inoperable. The suitability of corresponding to the region of the target gene containing the cleavage site, may be evaluated for GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA,

constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA sequences encoding CCYPR. Such DNA sequences may be incorporated into a wide variety of 32 Alternatively, RMA molecules may be generated by in vitto and in vivo transcription of DMA for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. by any method known in the art for the synthesis of nucleic acid molecules. These include techniques Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared

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cell lines, cells, or tissues.

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modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2'O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PUAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

RAA molecules may be modified to increase intracellular stability and half-life. Possible

An additional embodiment of the invention encompasses a method for screening for a

compounds which is effective in altering expression of a polynucleotide encoding CCYPR.

Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and nonsecromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased polynucleotide encoding CCYPR may be therapeutically inhibits expression of the associated with decreased CCYPR expression or activity, a compound which specifically promotes expression of the polynucleotide encoding CCYPR may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in At least one, and up to a plurality, of test compounds may be screened for effectiveness in

altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical someounds created combinatorially or randomly. A sample comprising a may comprise, for example, an intact or permeabilized cell, or an in vitto cell-free or reconstituted by any method commonly known in the expression of a polynucleotide encoding CCYPR are assayed detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding CCYPR. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide expression of a polynucleotide expression of a polynucleotide expression of a polynucleotide expression of a polynucleotide

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exposed to a test compound indicates that the test compound is effective in altering the expression of a specific the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a <u>Schizosaccharomyces pombe</u> gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Amdt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use <u>in vivo</u>, <u>in vitro</u>, and <u>ex vivo</u>. For <u>ex vivo</u> therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat.

Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and

An additional embodiment of the invention relates to the administration of a pharmaceutical

composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such edition of Remington's pharmaceutical compositions may consist of CCYPR, antibodies to CCYPR, and mimetics, agonists,

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal,

intranasal, enteral, topical, sublingual, or rectal means.

antagonists, or inhibitors of CCYPR.

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monkeys.

Pharmaceutical compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolat region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, 1.5. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of

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administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of pharmaceutical compositions may be prepared for direct intracellular

delivery of macromolecules comprising CCYPR or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, CCYPR or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs,

culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example

CCYPR or fragments thereof, antibodies of CCYPR, and agonists, antagonists or inhibitors of

CCYPR, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED<sub>20</sub> (the dose therapeutically effective in 50% of the population) or LD<sub>20</sub> (the dose tatio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD<sub>20</sub>/ED<sub>20</sub> ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED<sub>20</sub> with little or no toxicity. The dosage varies within this range depending upon the dosage form employed,

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular

the sensitivity of the patient, and the route of administration.

formulation.

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Normal dosage amounts may vary from about 0.1 µg to 100,000 µg, up to a total dose of

about I gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art.

Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells,

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conditions, locations, etc.

In another embodiment, antibodies which specifically bind CCYPR may be used for the diagnosis of disorders characterized by expression of CCYPR, or in assays to monitor patients being treated with CCYPR or agonists, antagonists, or inhibitors of CCYPR. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for CCYPR include methods which utilize the antibody and a label to detect CCYPR in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter without modification, and may be labeled by covalent or non-covalent attachment of a reporter be antibody and a label to detect and may be used.

known in the sart and provide a basis for diagnosing altered or abnormal levels of CCYPR expression.

Normal or standard values for CCYPR expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to CCYPR under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of CCYPR expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

A variety of protocols for measuring CCYPR, including ELISAs, RIAs, and FACS, are

In another embodiment of the invention, the polynucleotides encoding CCYPR may be used include oligonucleotide sequences, for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of CCYPR may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess with disease. The diagnostic assay may be used to determine absence, presence, and excess on the diagnostic assay may be used to determine absence, presence, and excess by monitor regulation of CCYPR levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide of the one aspect, hybridization with PCR probes which are capable of detecting polynucleotide.

sequences, including genomic sequences, encoding CCYPR or closely related molecules may be used to identify nucleic acid sequences which encode CCYPR. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding CCYPR, allelic variants, or related

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Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the CCYPR encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:55-108 or from genomic sequences including promoters, enhancers, and introns of the CCYPR gene.

Means for producing specific hybridization probes for DNAs encoding CCYPR include the

cloning of polynucleotide sequences encoding CCYPR or CCYPR derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymenases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as <sup>32</sup>P or <sup>35</sup>S, or by enzymatic labels, variety of reporter groups, for example, by radionuclides such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like. Polynucleotide sequences encoding CCYPR may be used for the diagnosis of disorders

associated with expression of CCYPR. Examples of such disorders include, but are not limited to, an

myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' disorder such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a developmental extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, purpura, ulcerative colitis, uveitis, Wemer syndrome, complications of cancer, hemodialysis, and systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic Reitet's syndrome, theumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, 52 disorder (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, mixed connective tissue Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal noctumal lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with (APECED), bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic

immune disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spina bifida,

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encoding CCYPR may be used in Southern or northern analysis, dot blot, or other membrane-based salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, connective tissue disease (MCTD), myelofibrosis, paroxysmal noctumal hemoglobinuria, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed disease, impotence, carcinoma of the male breast, and gynecomastia; and a cell proliferative disorder cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's receptors, syndrome of 5 lpha-reductase, a disruption of spermatogenesis, abnormal sperm physiology, associated with Leydig cell tumors, androgen resistance associated with absence of androgen men, Leydig cell deficiency, male climacteric phase, germinal cell aplasia, hypergonadal disorders breast cancer, and fibrocystic breast disease; and, in post-menopausal women, osteoporosis; and, in gonadotropin deficiency, amenorrhea, galactorrhea, hermaphroditism, hirsutism and virilization, fibroid, autoimmune disorders, an ectopic pregnancy, teratogenesis, hyperprolactinemia, isolated ovarian disease, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine tubal disease, ovulatory defects, and endometriosis, perturbations of the menstrual cycle, polycystic gonadal steroid hormones such as: in women, abnormal prolactin production, infertility, including adenoma of the adrenal cortex, hypertension associated with alkalosis; disorders associated with associated complications; disorders associated with the adrenals such as hyperplasia, carcinoma, or (chronic hypercalemia); pancreatic disorders such as Type I or Type II diabetes mellitus and with bacterial infection; disorders associated with hyperparathyroidism including Conn disease disorders associated with hypothyroidism including goiter, myxedema, acute thyroiditis associated inappropriate antidiuretic hormone (ADH) secretion (SIADH) often caused by benign adenoma; trauma; disorders associated with hyperpituitarism including acromegaly, giantism, and syndrome of malformations, thrombosis, infections, immunological disorders, and complications due to head adenomas, infarction associated with pregnancy, hypophysectomy, aneurysms, vascular disorders of the hypothalamus and pituitary resulting from lesions such as primary brain tumors, disorders of immune cell activation; a cell signaling disorder including endocrine disorders such as anencephaly, craniorachischisis, congenital glaucoma, cataract, sensorineural hearing loss, and PCT/US00/19948

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that detect the presence of associated disorders, particularly those mentioned above. The nucleotide

microarrays utilizing fluids or tissues from patients to detect altered CCYPR expression. Such technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in

qualitative or quantitative methods are well known in the art.

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In a particular aspect, the nucleotide sequences encoding CCYPR may be useful in assays

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monitor the treatment of an individual patient. the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to sample indicates the presence of the associated disorder. Such assays may also be used to evaluate a control sample then the presence of altered levels of nucleotide sequences encoding CCYPR in the standard value. If the amount of signal in the patient sample is significantly altered in comparison to suitable incubation period, the sample is washed and the signal is quantified and compared with a sample from a patient under conditions suitable for the formation of hybridization complexes. After a sequences encoding CCYPR may be labeled by standard methods and added to a fluid or tissue

values is used to establish the presence of a disorder. obtained from samples from patients who are symptomatic for a disorder. Deviation from standard polynucleotide is used. Standard values obtained in this manner may be compared with values normal subjects with values from an experiment in which a known amount of a substantially purified amplification. Standard hybridization may be quantified by comparing the values obtained from sequence, or a fragment thereof, encoding CCYPR, under conditions suitable for hybridization or combining body fluids or cell extracts taken from normal subjects, either animal or human, with a CCYPR, a normal or standard profile for expression is established. This may be accomplished by

In order to provide a basis for the diagnosis of a disorder associated with expression of

days to months. successive assays may be used to show the efficacy of treatment over a period ranging from several patient begins to approximate that which is observed in the normal subject. The results obtained from hybridization assays may be repeated on a regular basis to determine if the level of expression in the Once the presence of a disorder is established and a treatment protocol is initiated,

to employ preventative measures or aggressive treatment earlier thereby preventing the development of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals development of the disease, or may provide a means for detecting the disease prior to the appearance overexpressed) in biopsied tissue from an individual may indicate a predisposition for the With respect to cancer, the presence of an abnormal amount of transcript (either under- or

enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide CCYPR may involve the use of PCR. These oligomers may be chemically synthesized, generated 30 Additional diagnostic uses for oligonucleotides designed from the sequences encoding

or further progression of the cancer.

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quantification of closely related DNA or RNA sequences. condition. Oligomers may also be employed under less stringent conditions for detection or CCYPR, and will be employed under optimized conditions for identification of a specific gene or encoding CCYPR, or a fragment of a polynucleotide complementary to the polynucleotide encoding

encoding CCYPR may be used to detect single nucleotide polymorphisms (SNPs). SNPs are In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences

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chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry of DNA and sequencing errors using statistical models and automated analyses of DNA sequence sequence. These computer-based methods filter out sequence variations due to laboratory preparation sequence of individual overlapping DNA fragments which assemble into a common consensus methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in highthese differences are detectable using gel electrophoresis in non-denaturing gels. In fSCCP, the differences in the secondary and tertiary structures of PCR products in single-stranded form, and from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SWPs in the DNA cause amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, oligonucleotide primers derived from the polynucleotide sequences encoding CCYPR are used to conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, disease in humans. Methods of SNP detection include, but are not limited to, single-stranded substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic

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rapid quantitation. interest is presented in various dilutions and a spectrophotometric or colorimetric response gives accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from Methods which may also be used to quantify the expression of CCYPR include radiolabeling

using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

In further embodiments, oligonucleotides or longer fragments derived from any of the

effective and display the fewest side effects may be selected for a patient based on his/her and effective treatment regimen for that patient. For example, therapeutic agents which are highly may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate monitor the activities of therapeutic agents in the treatment of disease. In particular, this information monitor progression/regression of disease as a function of gene expression, and to develop and determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to 30 used to identify genetic variants, mutations, and polymorphisms. This information may be used to Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript can be used in transcript imaging techniques which monitor the relative expression levels of large polynucleotide sequences described herein may be used as elements on a microarray. The microarray 52

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protein interactions, drug-target interactions, and gene expression profiles, as described above. be used as elements on a microarray. The microarray may be used to monitor or measure protein-

A particular embodiment relates to the use of the polynucleotides of the present invention to

Transcript images may be generated using transcripts isolated from tissues, cell lines, resultant transcript image would provide a profile of gene activity. invention or their complements comprise a subset of a plurality of elements on a microarray. The hybridization takes place in high-throughput format, wherein the polynucleotides of the present 10 transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridizing the polynucleotides of the present invention or their complements to the totality of 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Mumber quantifying the number of expressed genes and their relative abundance under given conditions and at gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of

Transcript images which profile the expression of the polynucleotides of the present as in the case of a tissue or biopsy sample, or in vitto, as in the case of a cell line. biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo,

In one embodiment, the toxicity of a test compound is assessed by treating a biological toxicological screening using toxicant signatures to include all expressed gene sequences. http://www.niehs.nih.gov/oc/news/toxchip.htm.) Therefore, it is important and desirable in Environmental Health Sciences, released February 29, 2000, available at prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of knowledge of gene function is not necessary for the statistical matching of signatures which leads to gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, comparison of expression data after treatment with different compounds. While the assignment of are used to normalize the rest of the expression data. The normalization procedure is useful for not altered by any tested compounds are important as well, as the levels of expression of these genes measurement of expression provides the highest quality signature. Even genes whose expression is expression information from a large number of genes and gene families. Ideally, a genome-wide those toxic properties. These fingerprints or signatures are most useful and refined when they contain compound has a signature similar to that of a compound with known toxicity, it is likely to share (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and compounds. All compounds induce characteristic gene expression patterns, frequently termed pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental invention may also be used in conjunction with in vitro model systems and preclinical evaluation of

sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples

are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present

obtained for definitive protein identification. polypeptide sequences of the present invention. In some cases, further sequence data may be comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the 52 cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by spots are partially sequenced using, for example, standard methods employing chemical or enzymatic compared to identify any changes in protein spot density related to the treatment. The proteins in the biological samples either treated or untreated with a test compound or therapeutic agent, are optical densities of equivalently positioned protein spots from different samples, for example, from density of each protein spot is generally proportional to the level of the protein in the sample. The staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical supra). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, separated by isoelectric focusing in the first dimension, and then according to molecular weight by separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the given conditions and at a given time. A profile of a cell's proteome may thus be generated by are analyzed by quantifying the number of expressed proteins and their relative abundance under proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, 10 pattern of protein expression in a particular tissue or cell type. Each protein component of a invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global

A proteomic profile may also be generated using antibodies specific for CCYPR to quantify the levels of CCYPR expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) Anal. Biochem. 270:103-111; Mendoze, L.G. et al. (1999) Biotechniques 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor

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correlation between transcript and protein abundances for some proteins in some tissues (Anderson, 1LtL0/10 OM PCT/US00/19948

alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to useful in the analysis of compounds which do not significantly affect the transcript image, but which N.L. and J. Seilhamer (1997) Electrophoresis 18:533-537), so proteome toxicant signatures may be

rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such

In another embodiment, the toxicity of a test compound is assessed by treating a biological

polypeptides of the present invention. the amino acid residues of the individual proteins and comparing these partial sequences to the response to the test compound in the treated sample. Individual proteins are identified by sequencing sample. A difference in the amount of protein between the two samples is indicative of a toxic each protein is compared to the amount of the corresponding protein in an untreated biological biological sample are separated so that the amount of each protein can be quantified. The amount of sample containing proteins with the test compound. Proteins that are expressed in the treated

protein between the two samples is indicative of a toxic response to the test compound in the treated sample is compared with the amount in an untreated biological sample. A difference in the amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological incubated with antibodies specific to the polypeptides of the present invention. The amount of sample containing proteins with the test compound. Proteins from the biological sample are In another embodiment, the toxicity of a test compound is assessed by treating a biological

sample.

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In another embodiment of the invention, nucleic acid sequences encoding CCYPR may be (1999) Oxford University Press, London, hereby expressly incorporated by reference. well known and thoroughly described in DAA Microarrays: A Practical Approach, M. Schena, ed. 2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g.,

(BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific members of a multi-gene family may potentially cause undesired cross hybridization during be preferable over coding sequences. For example, conservation of a coding sequence among Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may used to generate hybridization probes useful in mapping the naturally occurring genomic sequence.

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WO 01/07471 et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J.

et al. (1997) Nat. Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, <u>supra</u>, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding CCYPR on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic

linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:5777-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between CCYPR and the agent being tested may be measured.

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Another technique for drug screening provides for high throughput screening of compounds

In another embodiment of the invention, CCYPR, its catalytic or immunogenic fragments, or

having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with CCYPR, or fragments thereof, and washed. Bound CCYPR is then detected by methods well known in the art. Purified CCYPR can also be coated directly onto plates for use in the aforementioned drug screening techniques.

Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding CCYPR specifically compete with a test compound for binding

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CCYPR. In this manner, antibodies can be used to detect the presence of any peptide which shares

In additional embodiments, the nucleotide sequences which encode CCYPR may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific

description, utilize the present invention to its funest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/145,075, U.S. Ser. No. 60/153,129, and U.S. Ser. No. 60/164,647, are hereby expressly incorporated by reference.

## **EXYMPPLES**

I. Construction of cDNA Libraries

one or more antigenic determinants with CCYPR.

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RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA

purity. In some cases, RMA was treated with DNase. For most libraries, poly(A+) RMA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEM, Chatsworth CA), or an OLIGOTEX mRMA purification kit (QIAGEM). Alternatively, RMA was isolated directly from tissue lysates using other RMA isolation kits, e.g., the POLY(A)PURE mRMA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA

1000 bp) using SEPHACRYL \$1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs

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SOLR from Stratagene or DH5a, DH10B, or ElectroMAX DH10B from Life Technologies. plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), pcDMA2.1 plasmid were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g.,

#### .II. Isolation of cDNA Clones

ml of distilled water and stored, with or without lyophilization, at 4°C. plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, 01 at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an excision using the UMIXAP vector system (Stratagene) or by cell lysis. Plasmids were purified using Plasmids obtained as described in Example I were recovered from host cells by in vivo

scanner (Labsystems Oy, Helsinki, Finland). using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically cycling steps were carried out in a single reaction mixture. Samples were processed and stored in high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal

#### Sequencing and Analysis щ 70

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2200 (Hamilton) liquid transfer system. cDAA sequencing reactions were prepared using reagents 52 Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MI Sequencing reactions were processed using standard methods or high-throughput instrumentation

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows.

Alternatively, plasmid DMA was amplified from host cell lysates using direct link PCR in a

Example VI. 7.7). Some of the cDMA sequences were selected for extension using the techniques disclosed in cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit calling software; or other sequence analysis systems known in the art. Reading frames within the or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI

using a combination of software programs which utilize algorithms well known to those skilled in the The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed

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art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software coftware Engineering, South San Francisco CA) and LASERGENE software parameters used to evaluate the strength of a match between two sequences (the higher the score, the software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software parameters used to evaluate the strength of a match between two sequences of the higher the score, the software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software parameters used to evaluate the strength of a match between the score, the score, the homology between two sequences.

sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire into full length polynucleotide sequences using programs based on Phred, Phrap, and EASTA and BLIMPS. The sequences were assembled were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, BOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene

The polynucleotide sequences were validated by removing vector, linker, and polyA

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:55-108. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

IV. Analysis of Polynucleotide Expression

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Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, <u>supra</u>, ch. 7; Ausubel, 1995, <u>supra</u>, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is

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much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

BLAST Score x Percent Identity

5 x minimum {length(Seq. 1), length(Seq. 2)}

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding CCYPR occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

# V. Chromosomal Mapping of CCYPR Encoding Polynucleotides

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sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:55-108 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences

The cDNA sequences which were used to assemble SEQ ID NO:55-108 were compared with

WO 01/07471 PCT/US00/19948 had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment

of all sequences of that cluster, including its particular SEQ ID NO:, to that map location.

The genetic map locations of SEQ ID MO:73, SEQ ID MO:73, SEQ ID MO:74, SEQ ID MO:75, SEQ ID MO:76, SEQ ID MO:77, SEQ ID MO:77, SEQ ID MO:77, SEQ ID MO:78, SEQ ID MO:90, and SEQ ID MO:105 are described in The Invention as ranges, or intervals, of human chromosomes. More than one map location is reported for SEQ ID MO:76, SEQ ID MO:77, SEQ ID MO:90, and SEQ ID MO:77, SEQ ID MO:77

(The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (http://www.ncbi.nlm.nih.gov/genemap/), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

## VI. Extension of CCYPR Encoding Polynucleotides

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The full length nucleic acid sequences of SEQ ID NO:55-108 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using ollido 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would tesult in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one

extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg<sup>2+</sup>, (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>,

mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg<sup>2+</sup>, (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Ptu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the

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alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times;

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN, quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviII cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For aparose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in

(Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Gtep 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethyaulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM primers and the DYENAMIC Equencing ready reaction kit (PE Biosystems).

The cells were lysed, and DMA was amplified by PCR using Taq DMA polymerase

384-well plates in LB/2x carb liquid media.

Step 6: 68°C, 5 min; Step 7: storage at 4°C.

the sequence.

In like manner, the polynucleotide sequences of SEQ ID NO:55-108 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

VII. Labeling and Use f Individual Hybridizati n Pr bes
Hybridization probes derived from SEQ ID NO:55-108 are employed to screen cDNAs,

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genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide

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hybridization analysis of human genomic DNA digested with one of the following endonucleases: An aliquot containing 10' counts per minute of the labeled probe is used in a typical membrane-based SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). (DuPont NEM, Boston MA). The labeled oligonucleotides are substantially purified using a [4-32P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 µCi of fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06

compared. Hybridization patterns are visualized using autoradiography or an alternative imaging means and under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature membranes (Mytran Plus, Schleicher & Schuell, Durham MH). Hybridization is carried out for 16 The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon

#### Microarrays ,ШУ

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described in detail below.

Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; 52 those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., procedures. A typical array may be produced using available methods and machines well known to elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding Alternatively, a procedure analogous to a doffor slot blot may also be used to arrange and link supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. 50 aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), The linkage or synthesis of array elements upon a microarray can be achieved utilizing

Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

on the microarray may be assessed. In one embodiment, microarray preparation and usage is complementarity and the relative abundance of each polynucleotide which hybridizes to an element 32 desorbtion and mass spectrometry may be used for detection of hybridization. The degree of fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser After hybridization, nonhybridized nucleotides from the biological sample are removed, and a biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the selected using software well known in the art such as LASERGENE software (DNASTAR). The comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may

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Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and

#### Tissue or Cell Sample Preparation

poly(A)\* RNA is purified using the oligo-(dT) cellulose method. Each poly(A)\* RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/µl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/µl RNase inhibitor, 500 µM dATP, 500 µM dGTP, 500 µM dTTP, 40 µM dCTP, 40 µM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)\* RNA with CEMBRIGHT kits (Incyte). Specific control poly(A)\* RNAs are synthesized by in vito transcription from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one incubated for 20 minutes at 85°C to the stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration and degrade the RNA. Samples are purified (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and safer combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and safer combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated (CLONTECH), Palo Alto CA) and after combining the complete in the complet

#### Microarray Preparation

resuspended in 14 µl 5X SSC/0.2% SDS.

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Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 ng. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope

Array elements are applied to the coated glass substrate using a procedure described in US patent No. 5,807,522, incorporated herein by reference. I µl of the array element DNA, at an average concentration of 100 ng/µl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene).

Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate

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WO 01/07471 PCT/US00/19948 buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in

0.2% SDS and distilled water as before.

#### <u>Mybridization</u>

Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 µl of 5X SSC in a comer of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

### <u>Detection</u>

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Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

Reporter-labeled hybridization complexes are detected with a microscope equipped with an

Hybridization reactions contain 9 µl of sample mixture consisting of 0.2 µg each of Cy3 and

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially.

Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477,

Hamamatsu Photonics Systems, Bridgewater MJ) corresponding to the two fluorophores. Appropriate
filters positioned between the array and the photomultiplier tubes are used to filter the signals. The
emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is
typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source,
slthough the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a

the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital

cDNA control species added to the sample mixture at a known concentration. A specific location on

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(A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectram.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

#### IX. Complementary Polynucleotides

Sequences complementary to the CCYPR-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring CCYPR. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of CCYPR. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the CCYPR-encoding complementary oligonucleotide is designed to prevent ribosomal binding to the CCYPR-encoding

Expression and purification of CCYPR is achieved using bacterial or virus-based expression

#### X. Expression of CCYPR

transcript.

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Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. 32 infect Spodopiera frugiperda (SP9) insect cells in most cases, or human hepatocytes, in some cases. polyhedrin promoter drives high levels of cDMA transcription. Recombinant baculovirus is used to transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong replaced with cDNA encoding CCYPR by either homologous recombination or bacterial-mediated (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is insect or mammalian cell lines with recombinant <u>Autographics californica</u> nuclear polyhedrosis virus thiogalactopyranoside (IPTG). Expression of CCYPR in eukaryotic cells is achieved by infecting Antibiotic resistant bacteria express CCYPR upon induction with isopropyl beta-Delement. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). promoter and the T5 or T7 bacteriophage promoter in conjunction with the lac operator regulatory transcription. Examples of such promoters include, but are not limited to, the trp-lac (tac) hybrid 52 containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA systems. For expression of CCYPR in bacteria, cDNA is subcloned into an appropriate vector

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et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther.

7:1937-1945.)
In most expression systems, CCYPR is synthesized as a fusion protein with, e.g., glutathione

S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step,

kilodalton enzyme from <u>Schistosoma japonicum</u>, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from CCYPR at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman resins (QIAGEM). Methods for protein expression and purification are discussed in Ausubel (1995, purification using commercially available by these methods can be used directly in the assays resins (QIAGEM). Purified CCYPR obtained by these methods can be used directly in the assays shown in Examples XI and XV.

#### 15 XI. Demonstration of CCYPR Activity

An assay for CCYPR activity measures cell proliferation as the amount of newly initiated DNA synthesis in Swiss mouse 3T3 cells. A plasmid containing polynucleotides encoding CCYPR is transfected into quiescent 3T3 cultured cells using methods well known in the art. The transiently transfected cells are then incubated in the presence of [<sup>3</sup>H]thymidine, a radioactive DNA precursor.

Where applicable, varying amounts of CCYPR ligand are added to the transfected cells.

Incorporation of [<sup>3</sup>H]thymidine into acid-precipitable DNA is measured over an appropriate time interval, and the amount incorporated is directly proportional to the amount of newly synthesized

### DNA and CCYPR activity. XII. Functional Assays

CCYPR function is assessed by expressing the sequences encoding CCYPR at physiologically elevated levels in mammalian cell culture systems. cDIAA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDIAA mammalian expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are co-transfected cells and is a reliable predictor of cDIAA expression from the recombinant vector. Marker proteins of cDIAA expression from the recombinant vector. Marker proteins of cDIAA expression from the recombinant vector. Marker proteins of cDIAA expression (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptoric state of the cells and other cellular properties. FCM detects CD64-GFP and to evaluate the apoptoric state of the cells and other cellular properties. FCM detects

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and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry. Oxford, New York NY.

The influence of CCYPR on gene expression can be assessed using highly purified

populations of cells transfected with sequences encoding CCYPR and either CD64 or CD64-GFP.

CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding CCYPR and other genes of interest can be analyzed by

#### XIII. Production of CCYPR Specific Antibodies

northern analysis or microarray techniques.

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CCYPR substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the CCYPR amino acid sequence is analyzed using LASERGENE software

(DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, <a href="mailto:supra">supra</a>.) Rabbits are immunized with the oligopeptide-immunogenicity. (See, e.g., Ausubel, 1995, <a href="mailto:supra">supra</a>.) Rabbits are immunized with the oligopeptide-cCYPR activity by, for example, binding the peptide or CCYPR to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG. XIV. Purification 1 Naturally Occurring CCYPR Using Specific Antibodies

XIV. Purification 1 1 Naturally Occurring CCYPR Using Specific Antibodies

XIV. Purification 1 1 Naturally Occurring CCYPR Using Specific Antibodies

chromatography using antibodies specific for CCYPR. An immunoaffinity column is constructed by covalently coupling anti-CCYPR antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is

Maturally occurring or recombinant CCYPR is substantially purified by immunosifinity

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blocked and washed according to the manufacturer's instructions.

Media containing CCYPR are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of CCYPR (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/CCYPR binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such

#### XV. Identification of Molecules Which Interact with CCYPR

as urea or thiocyanate ion), and CCYPR is collected.

CCYPR with the candidate molecules.

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(See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled CCYPR, washed, and any wells with labeled CCYPR complex are assayed. Data obtained using different concentrations of CCYPR are used to calculate values for the number, affinity, and association of

CCYPR, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent.

Alternatively, molecules interacting with CCYPR are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, Nature 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

CCYPR may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

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 Table

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10 Polypeptide 12 님 NO: 65 64 61 60 59 57 56 SEO Nucleotide U NO: 2049176 Clone 3500375 3215187 2686765 1988468 1887228 1752768 1416289 1210462 1558289 .577739 1305252 16462 IJ LUNGNOT23 LUNGAST01 BRSTNOT02 Library PROSTUT13 LIVRFET02 BLADTUT07 LIVRTUT01 SPLNNOT04 BRAINOT12 KIDNNOT01 TESTNOTO LNODNOT03 PLACNOT02 1502858F6 (BRAITUT07), 1956694X315D1 2022628X307D1 (CONNNOT01), 2686765F6 860585R1 (BRAITUT03), 072147R6 (THP1PEB01), 496297H1 (HNT2NOT01), 1: (LUNGNOT12), 1726095F6 (PROSNOT14), 1726095F6 080294F1 (SYNORAB01), (EOSIHET02), 516882R6 639958R6 (BRSTNOT03), 861752H1 (BRAITUT03), 1416289H1 2049176H1 1988468H1 (LUNGAST01), SBYA00612U1 1440718F6 (THYRNOT03), 256106R1 (HNT2RAT01), 181266R1 (PLACNOBO1), 1577739H1 (LNODNOTO3), 4180022T6 1558289H1 (SPLNNOT04), 3221088H1.comp 1703258T6.comp 260707H1 (HNT2RAT01), Fragments 2272329H1 3381980H1 (ESOGNOT04) (PROSNOT16 (COLNFET02), 1344279T6 (PROSNOT11), 1350089H1 (1440718F6 (THYRNOT03), 1752768F6 (LIVRTUT01), 4991290H1 (LIVRTUT11) (BRAINOT12), 794067R6 (OVARNOTO3), 871989R1 (LUNGASTO1), 151135R6 (FIBRAGT01), (LIVRTUT01), (SINITUT03), 4597046H1 (LUNGFET03), 1305252F6 (PLACNOT02), 1305252H1 (PLACNOT02), (KIDNNOTO9), LIVRFET02 TESTNOT07 LUNGNOT23), 887228H1 (BLADTUT07), THP1AZT01 BRAINOT12) 728643F6 COLNFET02), 1841248T6 KIDNNOT01), 16462H1 (KIDNNOT01) (PROSNONO1), (LIVRFET02), (SMCCNON03) 2864555H1 1483246F6 1752768T6 1416289X310B1 (BRAINOT12), 1416289X310D2 1500439F6 (SINTBST01), 2593267F6 1947451R6 (DUODNOT02), 2678307H1.comp (OVARTUT07), (COLNNON03) 3215187F6 258814H1 (HNT2RAT01), 1210462H1 (BRSTNOT02), 116462R1 1318501F1 140055F1 (TLYMNOR01), (MMLR1DT01), 1217892T1 (PITUNOT01 1988468T6 (LUNGAST01), 4323029H1 (TLYMUNTO1 (COLNNOT07), (KIDNNOT20), 2049176T6 (LIVRFET02), 2049176X321D1 5059810H1 (CONDTUT02) (COLSTUT01), 4860616H1 3209746F7 (CORPNOT02), (LIVRTUT01), 1852450T6 (LUNGFET03), (LUNGNOT22), 2632784F6 3647280H1 (ENDINOT01 (KIDNNOT01), (TESTNOT07), (BLADNOTO4), (BLADNOT08), 2079106F6 2369977F6 (ADRENOT07 2887609F6 2378362H1 (ISLTNOT01), 4614606H1 (LUNGNOT23), (CONNNOTO1), 285207X42 1235253F1 1312247F1 1362109F6 1458882F6 3215187H1 (NEUTGMT01), 16462X304D1 (SINJNOTO2), 2232471F6 (ISLINOTO1), (PROSTUT09), 2396092F6 3403213H1 419126F1 1752768H1 (LATRTUT02), (PANCTUT02), (PROSNOT14), (COLNTUT15 2686765H1

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## Table 1 (cont.)

		Clone ID	Library	Fragments
14	68	5080410	LNODNOT11	1270372X300D1 (BRAINOT09), 3460603H1 (293TF1T01), 5080410H1 (LNODNOT11)
15	69	5218248	BRSTNOT35	1 (PROSTUT12), 1808748X16C1 (PROS LUNGNOT28)
16	70	058336	MUSCNOT01	
17	71	1511488	LUNGNOT14	1 (PANCNOT08), 1511488H1 (LUNGNOT14), 14), 1850020F6 (LUNGFET03)
18	72	1638819	UTRSNOT06	(UTRSNOT06), 1), SBRA03813D
19	73	1655123	PROSTUT08	1271351F1 (TESTTUT02), 1353234F1 (LATRTUT02), 1655123H1 (PROSTUT08), 2132186R6 (OVARNOT03), 3296525H1 (TLYJINT01), 3354010H1 (PROSNOT28), 3741838F6 (MENTNOT01), 3741838T6 (MENTNOT01), SXAF03528V1
20	74	2553926	THYMNOT03	<b>— н</b>
21	75	2800717	PENCNOT01	411179F1 (BRSTNOT01), 415284R1 (BRSTNOT01), 1458971F1 (COLNFET02), 1600810H1 (BLADNOT03), 1622005F6 (BRAITUT13), 2173076F6 (ENDCNOT03), 2520087F6 (BRAITUT21), 2800717H1 (PENCNOT01), 5184583H1 (LUNGTMT03), 5435834H1 (SPLNNOT17), 5872662H1 (COLTDIT04)
22 23	76 77	5664154 017900	BRAUNOTO1 HUVELPB01	181534F1 (PLACNOB01), SCHA00262V1 017900H1 (HUVELPB01), 092858F1 (HYPONOB01), 1353543F1 (LATRTUT02), 1353543F6 (LATRTUT02), 1428464F1 (SINTBST01), q1616429
24	78	035102	HUVENOB01	035102H1 (HUVENOB01), 077722R1 (SYNORAB01), 995133H1 (KIDNTUT01), 1356968T6 (LUNGNOT09), 1963135R6 (BRSTNOT04), 2659921F6 (LUNGTUT09), 3110603H1 (BRSTNOT17)
25	79	259983	HNT2RAT01	983H1 (HNT2RAT01), ;
26	80	926810	BRAINOT04	0378T6 (EPIGNOT01), , SBIA04006D1, SBIA
27	81	1398816	BRAITUT08	056398F1 (FIBRNOT01), 1252138F2 (LUNGFET03), 1294556T1 (PGANNOT03), 1398816H1 (BRAITUT08), 1545328R1 (PROSTUT04)

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# Table 1 (cont.)

37	თ თ	35	34	33	32	31	30	29	28	Polypeptide SEQ ID NO:
91	90	89	88	87	86	85	84	83	82	Nucleotide SEQ ID NO:
1980010	1868749	1851534	1806850	1806454	1708229	1678765	1620092	1514559	1496820	Clone ID
LUNGTUT03	SKINBIT01	LUNGFET03	SINTNOT13	SINTNOT13	PROSNOT16	STOMFET01	BRAITUT13	PANCTUT01	PROSNON01	Library
127747R1 (TESTNOT01), 357561F1 (PROSNOT01), 357561R1 (PROSNOT01), 918017R1 (BRSTNOT04), 1428117F6 (SINTBST01), 1625080F6 (COLNPOT01), 1720753H1 (BLADNOT06), 1932038F6 (COLNNOT16), 1980010H1 (LUNGTUT03), 3112417F6 (BRSTNOT17), 4174704H1 (SINTNOT21), 4238802H1 (SYNWDIT01), 5499543H1 (BRABDIR01), g4337459	1 (BLADNOT04), 1398330F 08), 1868749F6 (SKINBIT 6 (PROSNON01), 2684670H 02), 4951533H2 (ENDVUNT 1 (BRAINOT19)	), 2407346R6 (BSTMNON02), H1 (BRADDIRO1), 5629312H1	270548H1 (HNT2NOT01), 443885R1 (MPHGNOT03), 1257235F1 (MENITUT03), 1337438H1 (COLNNOT13), 1351820F1 (LATRTUT02), 1544066R1 (PROSTUT04), 1806850F6 (SINTNOT13), 1806850H1 (SINTNOT13), 1984108T6 (LUNGAST01), 2921419H1 (SININOT04), 3109392H1 (BRSTTUT15)	406723H1 (EOSIHET02), 821556R1 (KERANOT02), 1649621F6 (PROSTUT09), 1710552H1 (PROSNOT16), 1806454F6 (SINTNOT13), 1806454H1 (SINTNOT13), 2526283H1 (BRAITUT21), 3869969H1 (BMARNOT03)	388493R1 (THYMNOT02), 1503519F1 (BRAITUT07), 1708229H1 (PROSNOT16), 1725267F6 (PROSNOT14), 3089258F6 (HEAONOT03)	1678765F6 (STOMFET01), 1678765H1 (STOMFET01), 2640786H1 (LUNGTUT08), 3542276F6 (TONSNOT03), 4180591H1 (SINITUT03), 4183383H1 (LIVRDIR01), 4349212H1 (TLYMTXT01), 4718559H1 (BRAIHCT02), 5023762H1 (OVARNON03), 5332272H1 (KIDNNOT34), g1665766	<u>6</u>	155768H1 (THP1PLB02), 1229952H1 (BRAITUT01), 1337018X11 (COLNNOT13), 1360361H1 (LUNGNOT12), 1365811H1 (SCORNON02), 1514559F6 (PANCTUT01), 1514559H1 (PANCTUT01)	996673H1 (KIDNTUT01), 1496820H1 (PROSNON01), 2368484F6 (ADRENOT07), 3071781X303D1 (UTRSNOR01), 3071781X307B1 (UTRSNOR01), 3071781X316D3 (UTRSNOR01)	Fragments

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### Table 1 (cont.)

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46	45	44	43	42	41	40	39	0	Polypeptide SEQ ID NO:
100	99	98	97	96	95	94	93	32	Nucleotide SEQ ID NO:
3520701	3082014	2959521	2797839	2683225	2668536	2456494	2359526	2006027	Clone ID
LUNGNON03	BRAIUNT01	ADRENOT09	NPOLNOT01	SINIUCT01	ESOGTUT02	ENDANOT01	LUNGFET05	OVARTUIOI	Library
971201H1 (MUSCNOT02), 1544657R6 (PROSTUT04), 1545570H1 (PROSTUT04), 1671030F6 (BMARNOT03), 1671030T6 (BMARNOT03), 2605263F6 (LUNGTUT07), 3520701H1 (LUNGNON03), 3520701R6 (LUNGNON03)	, Q	046696H1 (CORNNOTO1), 087727R6 (LIVRNOTO1), 138475H1 (LIVRNOTO1), 167505H1 (LIVRNOTO1), 647975H1 (CARCTXTO2), 781084T1 (MYOMNOTO1), 972191R6 (MUSCNOTO2), 1309196H1 (COLNFETO2), 2641117H1 (LUNGTUTO8), 2913953H1 (KIDNTUT15), 2959521H1 (ADRENOTO9), 2984654H1 (CARGDITO1), 2985141H1 (CARGDITO1), 3138371H1 (SMCCNOTO2), 3386016H1 (ESOGNOTO4), 3496187H1 (ADRETUTO7), 3614426H1 (EPIPNOTO1), 4287819H1 (LIVRDIRO1), 5395566H1 (LIVRTUT13), g505101	460779T6 (KERANOTO1), 782663H1 (MYOMNOTO1), 896898R1 (BRSTNOTO5), 1218533H1 (NEUTGMTO1), 1312923F6 (BLADTUTO2), 2473746F6 (THP1NOTO3), 2481564H1 (SMCANOTO1), 2797839H1 (NPOLNOTO1), 3350118H1 (BRAITUT24), 4184264H1 (BRABDIRO1), 4401265H1 (TESTTUTO3), 4727770H1 (GBLADITO1), 5080203H1 (LNODNOT11), 5524886H1 (LIVRDIRO1)	196443R6 (KIDNNOTO2), 1243440R6 (LUNGNOTO3), 1604540F6 (LUNGNOT15), 2072837H1 (ISLTNOTO1), 2683225F6 (SINIUCTO1), 2683225H1 (SINIUCTO1), 3647874H1 (ENDINOTO1), 4029178H1 (BRAINOT23)	1513847H1 (PANCTUT01), 1668943F6 (BMARNOT03), 1668943T6 (BMARNOT03), 1721443F6 (BLADNOT06), 2668536H1 (ESOGTUT02), 3438287H1 (PENCNOT05), SBFA00330F1, SCBA05255V1, SCBA01530V1	456494H1 EPIPNOT01	1667182F6 (BMARNOT03), 2359526H1 (LUNGFET05), 2359526X311D1 (LUNGFET05), 2555305F7 (THYMNOT03), 2654667T6 (THYMNOT04), SCHA00290V1, SCHA00266V1, g1748241	(SYNORATOS), 1418710F1 (KIDNNOTOS), 1204124H1 (SYNORATOS), 1418710F1 (KIDNNOTOS), 1697570T6 (BLADTUTOS), 1874051F6 (LEUKNOTO2), 2187960T6 (PROSNOT26), 2259032H1 (OVARTUTO1), 2259032R6 (OVARTUTO1), 3406237H1 (ESOGNOTO3), 3441729H1 (PENCNOTO6), 3555764H1 (LUNGNOT31), 3728010H1 (SMCCNONO3), 3813639H1 (TONSNOTO3), 4031501H1 (BRAINOT23), 4274704H1 (PROSTMTO1), 4602450H1 (BRSTNOTO7), g3327183	8

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Table 1 (cont.)

54	53	52	51	50	49	Polypeptide SEQ ID NO: 47
108	107	106	105	104	102	Nucleotide SEQ ID NO: 101
5992432	5682976	5678487	5627029	5040573	4764233 4817352	Clone ID 4184320
FTUBTUT02	BRAENOT02	293TF2T01	PLACFER01	COLHTUT01	PLACNOTO5 HELATXTO3	Library BRADDITO2
645878R6 (BRSTTUT02), 1287660F1 (BRAINOT11), 1287660T6 (BRAINOT11), 1417373F6 (BRAINOT12), 1618868F6 (BRAITUT12), 2269980R6 (UTRSNOT02), 2793117F6 (COLNTUT16), 3246793F6 (BRAINOT19), 3592787H1 (293TF5T01), 5992432H1 (FTUBTUT02), g821012	(LVENNOT01), 825361R1 (PROSNOT06), 8 )2), 1667502F6 (BMARNOT03), 1733323F6 5 (LEUKNOT02), 1963215T6 (BRSTNOT04), )1), 2896448H1 (KIDNTUT14), 3141553H1 5 (CONNTUT05), 3773427H1 (BRSTNOT25), 27), 5682976H1 (BRAENOT02), 5546853H1	1258787F6 (MENITUTO3), 1522008F1 (BLADTUTO4), 1597992F6 (BLADNOTO3), 2057679H1 (BEPINOTO1), 2411504H1 (BSTMNONO2), 2467956H1 (THYRNOTO8), 2739089F6 (OVARNOTO9), 2739089T6 (OVARNOTO9), 2740762H1 (BRSTTUT14), 2754616H1 (THP1AZS08), 3254971R6 (OVARTUNO1), 3487616H1 (EPIGNOTO1), 5678487H1 (293TF2TO1)	967988R1 (BRSTNOT05), 1534642T6 (SPLNNOT04), 1700904F6 (BLADTUT05), 1846971R6 (COLNNOT09), 2112727R6 (BRAITUT03), 2112727T6 (BRAITUT03), 2205225F6 (SPLNFET02), 2828475H1 (TLYMNOT03), 3439165F6 (PENCNOT06), 3604622H1 (LUNGNOT30)	1724126F6 (PROSNOT14), 1859337F6 (PROSNOT18), 2026289R6 (KERANOT02), 2026289T6 (KERANOT02), 2122846T6 (BRSTNOT07), 32225302H1 (ADRETUT07), 3322214H1 (PTHYNOT03), 4587178H1 (BRAQNOT01), 4601227H1 (BRSTNOT07), 4885408H1 (LUNLTMT01), 5040573H1 (COLHTUT01)	4764233H1 (PLACNOTO5), 5634642H1 (PLACFERO1), g1148809 426993R6 (BLADNOTO1), 426993T6 (BLADNOTO1), 488301R6 (HNT2AGTO1), 3779640H1 (BRSTNOT27), 4817352H1 (HELATXTO3)	(BRAINOT09), 4184253F6 (BRABDIR01), 1), 4184320H1 (BRADDIT02), 4252542F6

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mark-5 (g4107015)			S141 S142 T152		
			S109 S24 S59 S66	173	6
		N76	T34 S103 S5 T136	184	S
			S246 Y189		
	protein: E96-N297		S127 S176 T207		
ı	Germ cell-less	N74	T217 T82 S76	297	4
			S298		
		N306	564		
		NIGO NIGI	S246 S415 T142	418	L
	P120: E26-G293				,
	nucleolar protein				
	Proliferative cell				
			S234 T337		
	antigen: N117-K333				
	proliferating cell		7 S88		
- 1	P120 nuclear		T39 S190 S268	340	2
	domain: M1-R99				
Õ.	transduction-related				
	CICE signal				
	Protein SH3 domain				
	Q33				
-	Signal peptide: M1-	N15 N38	T10 S93	145	נק
		Sites	Sites	Residues	ID NO:
	Motifs and Domains	Glycosylation	Phosphorylation	Acid	tide SEQ
•	Signature Sequences	Potential	Potential	Amino	Polypep-

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Table 2 (cont.)

S358 S442 T446 S505 Y244	S442 T29 S72 S89	S7 S17 S65 T349	11 533 S227 S412 S505	Y240	T231 S242 Y106	T216 S225 S228	597 T	S152 T201 S210	T49				9 270	S445	T232 T288 S418	S190 S209 S210	S418 T80 S186	T288 T321 S328	T117 T125 S138	8 463 T237 S34 T67		У93	S305 S336 T578	S105 S153 T208	S493 T536 S45	S217 S339 T475	7 591 S582 T71 T208	דה אכ: אפמדמתפת מדרפת	מבולונים מולים
											-		N64 N94 N147							N208						N534 N585	N374 N425	Sites	
		1277	TRE oncogene: R56-		protein: V13-T117	Polyposis locus		homolog: G15-T117	Polyposis locus TB2									M1-E335	deformity:	Formin limb	TPR repeat V265-K516		control E239-P356	TPR domain mitosis		L64	Signal peptide M1-		
melanogaster	(g2286196) D.	related protein	TRE oncogene-			(g849238) H.	protein 1	polyposis locus	Similar to	M. musculus	protein (g2570051)	embryogenesis MRG1	Early			musculus	(g4101720) M.	related protein	specific formin	Lymphocyte				A. thaliana	homolog (g5541721)	cycle protein 23	Cell division		
	BLAST_GenBank	BLOCKS_DOMO	MOTIFS			BLAST_GenBank	BLAST_DOMO	BLAST_PRODOM	MOTIFS			BLAST_GenBank	MOTIFS				BLAST_GenBank	BLAST_DOMO	BLAST_PRODOM	MOTIFS			BLAST_GenBank	BLAST_DOMO	HMMR_PFAM	SPSCAN	MOTIFS	Databases	

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Table 2 (cont.)

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,	16	15	14	13	12	Polypep- tide SEQ ID NO:
162	168	199	165	531	160	Amino Acid Residues
S70 S85 T16 T28 T65 T80 T100 S127 Y111	1 S55 S6	S2 S21 S69 T102 S189	S3 T67 S104	S195 T196 S357 T45 S172 T199 S212 S322 S465 T495 T45 T241 S255 T279 T319 S328	S40	Potential Phosphorylation Sites
	N77			N244 N401		Potential Glycosylation Sites
·	Signal peptide M1-S61 H-Rev protein homolog P15-K166				Signal peptide: M1-A30  Transmembrane domain: A6-I29  Cornichon developmental protein: M1-S160	Signature Sequences, Motifs and Domains
growth and transformation dependent protein Rattus norvegicus	g3777529 retinoic acid receptor responder 3 Homo sapiens	Developmental protein DG1118 (g3789911) D. discoideum	Wolf-Hirschhorn syndrome candidate 2 protein (g3860187) H. sapiens	Cdc 73p (g632679) S. cerevisiae	Cornichon-like protein (g4521254) M. musculus	Homologous Sequences
BLAST-GenBank	BLAST-GenBank SPSCAN BLAST-PRODOM MOTIFS	MOTIFS BLAST_GenBank	MOTIFS BLAST_GenBank	MOTIFS BLAST_GenBank	MOTIFS SPSCAN HMMR BLAST_PRODOM BLAST_DOMO BLAST_GenBank	Analytical Methods and Databases

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Table 2 (cont.)

23 113 S88	22 128 S3	21 425 S122 S192 S218 T313 S370 S409 S241 Y399	20 280 T129 T119 S46 T S262	19 483 T394 S219 S298 S114 S371 T431	18 246 T209 T28 S136	Polypep- Amino Portide SEQ Acid Pho ID NO: Residues Si
8 T20 T37	S107	22 S235 T60 92 S203 S204 18 S226 S307 13 S332 S366 70 T375 T402 09 S89 S118 41 S284 T360 99	29 T6 T102 19 T181 S250 6 T72 T84 62	94 T85 S86 19 S225 T230 98 T299 T472 14 S200 T273 71 T407 T424	T209 S227 T243 T28 S223 S51 S136 S201	ation
	N42	N190 N311			N26 N158	Potential Glycosylation Sites
C125-P128 CVarian granulosa cell 13.0 KD protein HGR74 N16-P128 Biotin-requiring enzyme attachment site: L40-L90	Prenyl group binding		Signal peptide M1-L28	Signal peptide M1-G29 OS-9 precursor L54-E281	Protein cell intergenic region FTSJ K25-K241	Signature Sequences, Motifs and Domains
Mus musculus  LDOC-1 protein g3869127 (Homo sapiens) Nagasaki, K. et al. (1999) Cancer	g4580592	g455719 Activated c-raf oncogenic fusion protein homolog Homo sapiens	<u>g3901272</u> ZW10 interactor Zwint <u>Homo sapiens</u>	g1322234 OS-9 precursor Homo sapiens	g2622903 cell division protein J Methanobacterium thermoauto- trophicum	Homologous Sequences
BLAST-PRODOM BLAST-GenBank PROFILESCAN MOTIFS	BLAST-GenBank	BLAST-GenBank	BLAST-GenBank SPSCAN MOTIFS	BLAST-GenBank SPSCAN BLAST-PRODOM MOTIFS	BLAST-GenBank BLAST-PRODOM BLAST-DOMO MOTIFS	Analytical Methods and Databases

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[able 2 (cont.)

	(Homo sapiens)					
MOTIFS	g2276312					
BLAST-DOMO	CIP1	D7-P106, M1-N114				
BLAST-PRODOM	kinase inhibitor	kinase inhibitor:				
BLAST-GenBank	Cyclin dependent	Cyclin-dependent		T57	120	29
				S163		
MOTIFS				S105 S120 S133	•	
BLAST-DOMO	(Homo sapiens)	E4-Q185		1 T42		
BLAST_PRODOM	g6601438	S195-K353	N191	S85 S212 S283		
BLAST-GenBank	AF5q31 protein	af-4 (FEL protein):	N145 N157	S125 T42 S43	353	28
	(Homo sapiens)					
MOTIFS	gene-1 g4929330					
BLAST-GenBank	Hypoxia inducible			S11	93	27
	(Homo sapiens)			T89 T344 S364		
	g6179740			T383 S11 S49		
	brain antigen			S273 T376 T381		•
MOTIFS	cancer-testis-		N362	S109 S237 T269		
BLAST-GenBank	Paraneoplastic		N76 N107 N171	T344 S39 S78	402	26
MOTIFS	musculus)	Sushi domain: T165-C174		Y34		
BLIMPS-PFAM	Tera g1575505 (Mus	L86-V95		T89 S153 S197		
BLIMPS-PRINTS	expressed gene	signature:				
BLAST-GenBank	Teratocarcinoma	Annexin VI	N139	S145 S160 S217	221	25
	(1997) Genomics 46:397-408.					
MOTIFS	Lurquin, C. et al.	D91-A287				
BLAST-DOMO	(Homo sapiens)	D283,		S294 S300 Y127		
HMMER-PFAM	g4928044	м1-Q200, н205-		T55 S184 S226	-	
BLAST-PRODOM	associated gene 1	gene (MAGE) family:		S184 S246 S251		
BLAST-GenBank	Breast cancer	Melanoma antigen	N77	S95 T79 T98	308	24
Databases			Sites	Sites	Residues	ID NO:
Methods and	Sequences		Glycosylation	Phosphorylation	Acid	tide SEQ
Analytical	Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-

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Table 2 (cont.)

32	31	30	Polypep- tide SEQ ID NO:
268	933	144	Amino Acid Residues
S7 T104 T154 S169	\$603 T51 \$109 T129 \$162 \$203 \$223 \$224 \$240 \$261 \$266 \$280 \$282 \$313 T328 \$346 \$353 \$378 \$394 \$460 \$491 \$499 T531 \$627 \$641 \$642 \$725 T732 \$759 \$188 \$309 \$423 \$592 \$671 \$675 T706 \$771 \$856	S15 S64	Potential Phosphorylation Sites
N90	N107 N238 N639 N883		Potential Glycosylation Sites
Serine-Threonine kinase Binder MPS1: L74-I230		Transmembrane domain: 193-1110	Signature Sequences, Motifs and Domains
Putative mitotic protein (Schizosaccharomyc es pombe) g3947877 F.C.Luca and M.Winey (1998) Mol Biol Cell 9:29-46.	Replication protein Smp2 g218488 (Saccharomyces cerevisiae) Irie,K. et al. (1993) Mol. Gen. Genet. 6:283-288.	Transformation dependent protein g207250 (Rattus norvegicus) N.Glaichenhaus and F.Cuzin (1987) Cell 50:1081-1089.	Homologous Sequences
BLAST-GenBank BLAST-PRODOM MOTIFS	BLAST-GenBank MOTIFS	BLAST-GenBank MOTIFS HMMER	Analytical Methods and Databases

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Table 2 (cont.

	(1999) Oncogene 18:3799-3809.					
	(Homo sapiens) Koga, H. et al.			Y203		
	1(3)mbt   g3811111		-	S181 T192 T347		
MOTIFS	tumor protein			S108	495	36
	(Homo sapiens) Stecc I. et al. (1998) Hum. Mol. Genet. 7:1071- 1082.					
	syndrome critical region 1) g4378022			S213		
BLAST-GenBank MOTIFS	Predicted WHSC1 protein (Wolf-		N36 N94 N225	S200 T47 T62 S78 S107 S188 S192 S206 S200	228	35 5
		G254-1270		\$106 \$205 \$218 \$258 T297 \$314 T325 \$463 T470 Y460		
HMMER_PFAM BLIMPS-PRINTS MOTIFS	g7672734 (Homo sapiens)	H75-Y123, L82-N95 Disease resistance protein:	N506	T142 S245 S466		
BLAST-GenBank	F-box protein FLR1	F-Box domain:	N347 N386	S34 S6	565	34
MOTIFS	protein g184390 (Homo sapiens) Weitzel,J.N. et al. (1992) Genomics 14:309- 319.	L259-L280, L266-L287				
BIAST-GenRank	hinding	Leucine zinner:		TAP 25.05	227	22
Methods and Databases	Sequences	Motifs and Domains	Glycosylation Sites	Phosphorylation Sites	Acid Residues	tide SEQ
Analytical	Homologous		Potential	Potential	Amino	-מפת

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Table 2 (cont.)

Polypep-	Amino	Potential	Potential	Signature Sequences,	Homologous	Analytical
tide SEQ	Acid Residues	Phosphorylation Sites	Glycosylation Sites	Motifs and Domains	Sequences	Methods and Databases
37	1336	T635 T769 S902	N148 N152	Ribosomal protein	Neuroblastoma	BLAST-GenBank
		32 S	N345 N385	S14 signature:	related protein	BLIMPS-PRINTS
		S95 S156 T298	N1213 N1247	R1172-N1194	g4337460	MOTIFS
		S313 T427 S467		Leucine zipper:	(Homo sapiens)	
		T579 T626 T642		L211-L232		
		T668				
		<b>T729</b>				
		T859				
		S997 S1049				
		T1085 S1132				
		S1227 T1245				
		S1249 T48 S94				
		T169 S224 T352				
		T696 S867 T883				
		T889 S940 S961				
		I O				
38	934		N8 N210 N426	SAP:	Sap2 family	BLAST-GenBank
		T80 S171 S202		I92-Q364	putative cell	BLAST-DOMO
		T214 T240 S244			cycle dependent	MOTIFS
		T275 S412 S416			phosphatase	
		S437 S518 T523			g3426127	
		S719 S746 S753			(Schizosaccharomyc	
		S796 S807 S93			es pombe)	
		T279 T527 S598			Luke, M.M. et al.	
		T780			(1996)	
					Mol. Cell Biol.	
			i		16:2744-2755.	

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Table 2 (cont.)

								42 131 S78 T121 T26				S329 S340		S86 '	<b>S</b> 36			40 146 S61						T486 Y13 Y383	S215 T316 S457	T79 S139 T189		S272 S277 S305		ID NO: Residues Sites Sites	EQ ACIC PhosphoryLation	
							Q64-K75	Presenilin:						H19-K262	0 Cyclin:	L19-L40	L5-L26, L12-L33,	Leucine zipper:							L234-L255	Leucine zipper:	E65-R230	Associated Protein:	N16 N31 N115 Metastasis-	. es	Glycosylation   Motifs and Domains	
9:782-787.	Biol.	Curr. Opin. Cell	M.N.Hall (1997)	G.Thomas and	(Homo sapiens)	g4322559	regulator DRR1	Cell growth	18:4291-4300.	Mol. Cell Biol.	al. (1998)	Edwards, M.C. et	(Homo sapiens)	g3746549	Cyclin K	(Homo sapiens)	g3869127	LDOC1	269:22958-22963.	J Biol. Chem.	(1994)	Toh, Y, et al.	Gene 159:97-104	(1995)	Toh, Y. et al.	(Homo sapiens)	g1008544	associated gene	Metastasis		Sequences	
						MOTIFS	BLIMPS-PRINTS	BLAST-GenBank					MOTIFS	BLAST-PRODOM	BLAST-GenBank	MOTIFS	BLIMPS-PFAM	BLAST-GenBank								MOTIFS	BLIMPS-PRINTS	BLAST-PRODOM	BLAST-GenBank	Databases	Methods and	

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### Table 2 (cont.)

	(1994) J. Biol. Chem. 269:22958-22963.	P432-K555 Leucine zipper: L147-L168				
	Toh, Y. et al.	G340-G483,				
	Gene 159:97-104	D144-K321,				
_	(1995)	R19-R143,				
	Toh, Y. et al.	MTA1:				
	(Homo sapiens)	associated protein		T374 S412 T450		
MOTIFS	g1008544	Metastasis-				
BLAST-PRODOM	associated gene	C283-T288		S575		
BLAST-GenBank	Metastasis	Cytochrome C motif:	N28	S185 T324 S343	584	45
	(Homo sapiens)	W472-F490				
	g1256001	V271-L290,		S37 T45 T282		
MOTIFS	cancer LIV-1	I506-G532,		S356 T386 S485		
HMMER	protein in breast	domains:	N147			
BLAST-GenBank	Estrogen induced	Transmembrane	N122 N132	S505 T69 S138	537	44
		F587-G805				
		Т311,				
		M1-S134, E135-		S790 Y277		
		P120:		S708 T739 T776		
		Nucleolar Antigen		T695 S702 S707		
		Proliferating Cell		S562 S565 T566		
_		E189-M576		T316 T319 T505		
		K507-L532,		S40 T64 T311		
		F454-G467,		T542 T605 S675		
HMMER-PFAM		G410-G433,		T477 S497 T520		
MOTIFS		I388-M402,		S262 S279 S440		
BLIMPS-BLOCKS	sapiens)	F300-K585,		S150 S181 T185		
BLAST-DOMO	P120 g287723 (Homo	F454-G467,		S134 T140 S148		
BLAST-PRODOM	nuclear protein	family signature:		S801 S111 S120		7
BLAST-GenBank	Proliferating cell	NOL1/NOP2/fmu(sun)	N503 N618	S44 S588 S646	812	43
Databases			Sites	Sites	Residues	ID NO:
Methods and	Sequences	C.	Glycosylation	Phosphorylation	Acid	tide SEQ
Analytical	Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-

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Table 2 (cont.)

422	48 111	255	425	tide SEQ Acid ID NO: Residues
T110 T159 S136 S150 T163 T190 S383 T413 S9 T27 S46 S96 T347 S359 S363 S368 Y350	T30 S2 T8	T9 T147 S237	S190 T301 S12 S19 S41 S205 T206 T235 S263 S265 T315 S43 S52 S85 T93 T351 S411 Y422	Phosphorylation Sites
		N144	N275	Glycosylation Sites
XPMC2 (mitosis associated inducing protein): A236-E402		Melastatin: M1-R172, G199-G255	MLO2 mitosis- associated protein: L24-R188, P226-Y245, N308-E408	Motifs and Domains
Mitotic regulator XPMC2 (Xenopus gene which prevents mitotic catastrophe) g595380 (Xenopus laevis) J.Y.Su and J.L.Maller (1995) Mol. Gen. Genet. 246:387-396.	Melanoma associated antigen GAGE-8 g3511023 (Homo sapiens) Van den Eynde, B. et al. (1995) J. Exp. Med. 182:689-698.	Melastatin g3047242 (Mus musculus) Duncan, L.M. et al. (1998) Cancer Res. 58:1515-1520.		Sequences
BLAST-GenBank BLAST-PRODOM BLAST-DOMO MOTIFS	BLAST-GenBank MOTIFS	BLAST-GenBank BLAST-PRODOM MOTIFS	BLAST-PRODOM MOTIFS	Methods and Databases

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#### Table 2 (cont.)

52	51	Polypep- tide SEQ ID NO: 50
713		Amino Acid Residues 397
\$100 T631 S8 T9 \$20 T42 T114 T121 T172 T177 T191 T192 \$218 T231 T256 \$325 \$335 \$381 T464 T482 T538 T581 T617 \$693 \$94 \$166 T201 \$202 \$321 T568 \$614 T658 Y459	\$56 \$448 T721 \$760 \$48 \$84 \$111 \$119 T146 \$1189 T235 \$250 \$265 T275 \$321 \$335 T392 \$448 \$1466 \$474 T562 \$596 \$598 T626 \$686 \$3 \$4 \$65 \$89 \$107 T123 \$348 T398 T402 \$7716 \$730 \$738 \$7743 \$789 \$102 \$7316 \$7569 \$685	Potential Phosphorylation Sites S20 S21 T395 T57 S59 T64 S127 S208 T210 S262 S307 T341 T64 T168 S180 S185 S218 S231 S288 S326
N7 N49 N462	N554 N665	Potential Glycosylation Sites N222 N260
Leucine zipper: L680-L701	Signal peptide: M1-A25 Leucine zipper: L365-L386	Signature Sequences, Motifs and Domains Transmembrane motifs: I361-L380, L24-L44 Cell division control protein: K17-L347
Colon cancer antigen NY-CO-8 g3170180 (Homo sapiens) Scanlan, M.J. et al. (1998) Int. J. Cancer 76:652-658.	SART-1 g4126469 (Mus musculus)	Homologous Sequences Cell cycle protein CDC1 g550426 (Saccharomyces cerevisdiae)
BLAST-GenBank BLAST-PRODOM BLAST-DOMO MOTIFS	BLAST-GenBank SPSCAN MOTIFS	Analytical Methods and Databases BLAST-GenBank HMMER BLAST-PRODOM MOTIFS

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Table 2 (cont.

1.1.	3	Dot ontion	Dotontipl	Cignature Comiences	Homologous	Analytical
tide SEQ	Acid	Phosphorylation	Glycosylation	Motifs and Domains	Sequences	Methods and
ID NO:	Residues	Sites	Sites			Databases
53	880	S18 S68 T123	N60 N251 N338	MybI DNA-binding	homologous to	BLAST-GenBank
		T143 S159 T178	N514 N585	domain:	mouse gene PC326	BLAST-DOMO
		S294	N643	W808-I816	g458692	HMMER-PFAM
		S376 S388 T397		WD40 domains:	(Homo sapiens)	BLIMPS-PRINTS
		<b>S426</b>		L41-N79, K84-N124,	Bergsagel, P.L.	MOTIFS
		S474 S563 T587		T131-D170,	et al.	
		T634 T645 S659		G239-D281,	(1992)	
		S665 S677 S756		A771-S809,	Oncogene	
		S799 S809 T827		F157-T171	7:2059-2064.	
		S870 S82 T88		Acidic Serine		
		S99 T131 T165		Cluster Repeat:		
		\$215 \$253 \$362		A423-R697		
		S487 T510 S525				
		S589 T593 S622				
54	855	T460 S8 S179	N552	Crooked neck protein	Predicted TPR	BLAST-GenBank
		S261 T288 T313		(RNA processing	domain protein	BLAST-PRODOM
		T377 T706 T719		associated, contains	G2315362	MOTIFS
		T755 S764 S803		TPR repeat):	(Caenorhabditis	
		S851 S34 S67		W398-V814	elegans)	
		T129 S190 S339			Zhang, K. et al.	
		T391 S483 S502			(1991)	
		S537 Y92			Genes Dev.	
					5:1080-1091.	

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65 488 109	64 12-56	63 559	62 226	61 104	60 56-	59 406	58 226	57 100	56 406	55 263	Nucleotide Sel SEQ ID NO: Fra
488-532 1091-1135	-56	559-603	226-270	1046-1090	56-100	406-450	226-270	1001-1045	406-450	263-307	Selected Fragments
Reproductive (0.308) Nervous (0.282) Gastrointestinal (0.154)	Reproductive (0.385) Gastrointestinal (0.231) Cardiovascular (0.154) Nervous (0.154)	Reproductive (0.260) Gastrointestinal (0.145) Cardiovascular (0.130)	Hematopoietic/Immune (0.288) Nervous (0.178) Reproductive (0.164)	Nervous (0.271) Reproductive (0.220) Gastrointestinal (0.153)	Gastrointestinal (0.545) Nervous (0.182) Reproductive (0.182)	Hematopoietic/Immune (0.500) Cardiovascular (0.227)	Nervous (0.316) Hematopoietic/Immune (0.211) Reproductive (0.211)	Reproductive (0.265) Gastrointestinal (0.206) Nervous (0.206)	Reproductive (0.222) Cardiovascular (0.167) Gastrointestinal (0.167) Nervous (0.167)	Cardiovascular (0.200) Gastrointestinal (0.200) Reproductive (0.200)	Tissue Expression (Fraction of Total)
Cancer (0.487) Inflammation (0.231) Cell Proliferation (0.103)	Cancer (0.538) Inflammation (0.154) Cell Proliferation (0.154)	Cancer (0.458) Inflammation (0.359) Cell Proliferation (0.176)	Cancer (0.397) Inflammation (0.548)	Cancer (0.542) Inflammation (0.288) Cell Proliferation (0.220)	Cancer (0.545) Inflammation (0.364) Cell Proliferation (0.273)	Cancer (0.182) Inflammation (0.682) Cell Proliferation (0.136)	Cancer (0.368) Inflammation (0.368) Cell Proliferation (0.158)	Cancer (0.412) Inflammation (0.324) Cell Proliferation (0.176)	Cancer (0.500) Inflammation (0.389) Cell Proliferation (0.167)	Cancer (0.433) Inflammation (0.267) Cell Proliferation (0.200)	Disease or Condition Fraction of Total
PINCY	PINCY	PSPORT1	PINCY	PINCY	PINCY	PINCY	PINCY	PINCY	PSPORT1	PBLUESCRIPT	Vector

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able 3 (cont.)

	73				74				73				72			71		70			69				88			67			66	SEQ ID NO:	Nucleotide
	535-579	241_285			651-695			1066-1110	106-150				604-648			164-208		77-121			64-108				451-495		1136-1180	326-370			37-81	Fragments	Selected
	(0.169) Gastrointestinal (0.157)		(0.161)	Reproductive (0.226) Cardiovascular	-		Cardiovascular (0.114)	Nervous (0.202)	Reproductive (0.307)		Hematopoietic/Immune (0.128)	Gastrointestinal (0.149)	Reproductive (0.362)		$\sim$	Developmental (0.222)	Musculoskeletal (0.500)	Cardiovascular (0.500)	(0.140)	Nervous (0.174) Cardiovascular	Reproductive (0.233)	Hematopoietic/Immune (0.125)		Reproductive (0.312) Developmental	Nervous (0.312)	Hematopoietic/Immune (0.158)	Reproductive (0.237)	Nervous (0.237)	(0.250)	Dermatologic (0.250) Reproductive	Nervous (0.500)	(Fraction of Total)	Tissue Expression
cert profferation (0.169)	Inflammation/Trauma	Cancer (0 458)	Cancer (0.320)	(0.451)	Inflammation/Trauma	Cell proliferation (0.175)	(0.307)	Inflammation/Trauma	Cancer (0.482)	Cell proliferation (0.170)	(0.276)	Inflammation/Trauma	Cancer (0.426)	Trauma (0.222)	Cell proliferation (0.222)	Cancer (0.444)	Trauma (0.500)	Cancer (0.500)	Cell Proliferation (0.198)	Inflammation (0.279)	Cancer (0.477)		Cell Proliferation (0.312)	Inflammation (0.188)		Cell Proliferation (0.158)	Inflammation (0.316)	Cancer (0.395)			Inflammation (0.500)	n Of	Disease or Condition
	DINCI	DINCY			PINCY				PINCY				DINCY			PINCY .		PBLUESCRIPT			PINCY				PINCY			PINCY			pINCY		Vector

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Table 3 (cont.)

	85	84	& 		82	81	80	79	78	77	76	Nucleotide SEQ ID NO:
	124-168	342-386	177-221		150-194	149-194	870-914	79-123	176-220	13-57	173-217 593-637	Selected Fragments
Gastrointestinal (0.154)	Hematopoietic/Immune (0.308) Cardiovascular (0.154)	Reproductive (0.252) Gastrointestinal (0.196) Nervous (0.161)	Reproductive (0.199) Gastrointestinal (0.173) Hematopoietic/Immune (0.128) Nervous (0.128)	Hematopoietic/Immune (0.125) Developmental (0.125) Urologic (0.125)	Reproductive (0.375) Cardiovascular (0.125) Endocrine (0.125)	Nervous (0.216) Reproductive (0.201) Gastrointestinal (0.185)	Nervous (0.571) Reproductive (0.238) Developmental (0.095)	Nervous (0.280) Cardiovascular (0.160) Developmental (0.160)	Nervous (0.279) Reproductive (0.235) Gastrointestinal (0.147)	Reproductive (0.241) Nervous (0.202) Cardiovascular (0.140)	Nervous (0.513) Reproductive (0.167)	Tissue Expression (Fraction of Total)
	Cancer (0.538) Inflammation (0.308)	Cancer (0.483) Inflammation (0.238) Cell Proliferation (0.161)	Cancer (0.429) Inflammation (0.270) Cell Proliferation (0.186)		Cancer (0.375) Inflammation (0.375) Trauma (0.250)	Cancer (0.432) Inflammation (0.259) Cell Proliferation (0.154)	Cancer (0.238) Inflammation (0.381) Cell Proliferation (0.190)	Cancer (0.480) Cell Proliferation (0.480) Inflammation (0.160)	Cancer (0.500) Inflammation (0.176) Cell Proliferation (0.162)	Cancer (0.461) Inflammation (0.180) Cell Proliferation (0.167)	Inflammation/Trauma (0.371) Cancer (0.333) Cell proliferation (0.141)	Disease or Condition Fraction of Total
	PINCY	PINCY	PINCY		PSPORT1	PINCY	PSPORT1	PBLUESCRIPT	PBLUESCRIPT	PBLUESCRIPT	PINCY	Vector

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Table 3 (cont.)

	96 465-509			95 1173-1217			94 . 126-170				93 761-805			92 489-533			91 72-116		879-923	90 69-113			352-396	184-228			88 -621 88				117-161			238-282	SEQ ID NO: Fragments	Nucleotide   Selected
Cardiovascular (0.158) Gastrointestinal (0.145)	Hematopoietic/Immune (0.250)		Gastrointestinal (0.192)	Reproductive (0.192)	Developmental (0.138)	Nervous (0.241)	Reproductive (0.379)		Developmental (0.125)	Hematopoietic/Immune (0.156)	Reproductive (0.219)	Gastrointestinal (0.123)	Nervous (0.217)	Reproductive (0.274)	Gastrointestinal (0.158)	Reproductive (0.197)	Nervous (0.211)	Hematopoietic/Immune (0.158)	Reproductive (0.193)	Nervous (0.316)	Developmental (0.111)	Hematopoietic/Immune (0.111)	Nervous (0.222)	Reproductive (0.556)	Gastrointestinal (0.168)	Reproductive (0.214)	Nervous (0.237)		Hematopoietic/Immune (0.115)	Gastrointestinal (0.250)	Reproductive (0.250)	Nervous (0.169)	Cardiovascular (0.181)	Reproductive (0.277)	(Fraction of Total)	Tissue Expression
	Inflammation (0.368)	Cell Proliferation(0.212)		Cancer (0.481)	Inflammation (0.103)	Cell Proliferation(0.241)	Cancer (0.414)	Trauma (0.188)	Inflammation (0.188)	Cell Proliferation(0.281)	Cancer (0.312)	Cell Proliferation(0.160)	Inflammation (0.189)	Cancer (0.481)	Cell Proliferation(0.211)	Inflammation (0.263)	Cancer (0.461)	Cell Proliferation(0.123)	Inflammation (0.211)	Cancer (0.439)		Cell Proliferation(0.333)	Inflammation (0.333)	Cancer (0.444)	Trauma (0.137)	Inflammation (0.298)	Cancer (0.397)	Trauma (0.115)	Cell Proliferation (0.115)	Inflammation (0.192)	Cancer (0.558)	Cell Proliferation (0.157)	Inflammation (0.193)	Cancer (0.434)	Fraction of Total	Disease or Condition
	pINCY		•	PINCY			PBLUESCRIPT				PSPORT1			PSPORT1			PSPORT1			PINCY				PINCY			PINCY				PINCY			PINCY		Vector

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Table 3 (cont.)

107	101		106				105			104			103	102			101						100			99			98.			97	SEQ ID NO:	Nucleotide
16/-211 814-859 1922-1966	163 011	513-557	255-299						908-952	413-457			199-243	8-52			861-905					460-504	73-117			106-150			23-67			2427-2471	Fragments	Selected
Reproductive (0.263) Nervous (0.162) Gastrointestinal (0.141)	Nervous (0.157)	Gastrointestinal (0.196)	Reproductive (0.216)	Developmental (0.101)	Hematopoietic/Immune 0.101)	Gastrointestinal (0.169)	Reproductive (0.270)	Gastrointestinal (0.125)	Reproductive (0.222)	Nervous (0.236)	Reproductive (0.286)	Nervous (0.179)	Hematopoietic/Immune (0.143)	Developmental (1.000)		Nervous (0.667)	Developmental (0. 333)	Musculoskeletal (0.105)	Gastrointestinal (0.105)	Developmental (0.105)	Cardiovascular (0.105)	Reproductive (0.211)	Hematopoietic/Immune (0.211)	Nervous (0.158)		Gastrointestinal (0.263)	Cardiovascular (0.135)	Reproductive (0.190)	Gastrointestinal (0.270)	Gastrointestinal (0.184)	Reproductive (0.197)	Nervous (0.224)		Tissue Expression
Inflammation (0.202) Trauma (0.131)		Inflammation (0.176)	Cancer (0.490)		Cell Proliferation(0.258)	Inflammation (0.281)	Cancer (0.449)	Cell Proliferation(0.139)	Inflammation (0.236)	Cancer (0.458)		Inflammation (0.250)	Cancer (0.536)	Cell Proliferation (1.000)	Neurological (0.333)	Trauma (0. 333)	Cell Proliferation(0, 333)				Cell Proliferation(0.211)	Inflammation (0.263)	Cancer (0.474)	Cell Proliferation(0.211)	Inflammation (0.368)	Cancer (0.474)	Cell Proliferation(0.143)	Inflammation (0.278)	Cancer (0.429)	Inflammation (0.237)	Cell Proliferation(0.263)	Cancer (0.474)	Fraction of Total	Disease or Condition
PINCX	TWOV		PINCY				PINCY			PINCY			PINCY	PINCY			PINCY						PSPORT1			PINCY			PINCY			PINCY		Vector

**ΔC1/Ω200/16648** 

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Table 3 (cont.)

Nucleotide   Selected	Selected	on	Disease or Condition	Vector
SEQ ID NO	SEQ ID NO: Fragments	(Fraction of Total)	Fraction of Total	
108	877-921	Reproductive (0.299)	Cancer (0.536)	PINCY
	2230-2274	Nervous (0.206)	Inflammation (0.227)	
		Gastrointestinal (0.134)	Cell Proliferation(0.124)	

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#### able 4

58	59	59
	BRAINOT12 SPLNNOT04	BRAINOT12 SPLNNOT04 LNODNOT03
	Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. Family history included a cervical neoplasm.  Library was constructed using RNA isolated from the spleen tissue of a 2-year-old Hispanic male, who died from cerebral anoxia.	using RNA isolated from br c-old Caucasian male during microgyria and mild to mod , which are consistent wit ical neoplasm.  using RNA isolated from th from cerebral anoxia.  using RNA isolated from ly during a segmental lung re cissue was found to be exterissue was found to be exterissue in patient history included coronary artery disease, lerotic coronary artery disease
		LINODNOTO3  Library was constructed using RNA isolated from lymph node tissue obtained from a year-old Caucasian male during a segmental lung resection and bronchoscopy. On microscopic exam, this tissue was found to be extensively necrotic with 10% viable tumor. Pathology for the associated tumor tissue indicated invasive grade 3-4 squamous cell carcinoma. Patient history included hemangioma. Family history included atherosclerotic coronary artery disease, benign hypertension, congestive heart failure, atherosclerotic coronary artery disease.

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# Table 4 (cont.)

26 57 86
LNODNOT11
Library was constructed using RNA isolated from lymph node tissue removed from a 16-

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# Table 4 (cont.)

		86				
74	73	72	71	70	69	Nucleotide SEQ ID NO:
THYMNOT03	PROSTUT08	UTRSNOT06	LUNGNOT14	MUSCNOT01	BRSTNOT35	Library
Library was constructed using RNA isolated from thymus tissue removed from a 21-year-old Caucasian male during a thymectomy. Pathology indicated an unremarkable thymus and a benign parathyroid adenoma in the right inferior parathyroid. Patient history included atopic dermatitis, a benign neoplasm of the parathyroid, and tobacco use. Family history included atherosclerotic coronary artery disease and benign hypertension.	Library was constructed using RNA isolated from prostate tumor tissue removed from a 60-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 3+4). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Patient history included a kidney cyst, and hematuria. Family history included tuberculosis, cerebrovascular disease, and arteriosclerotic coronary artery disease.	Library was constructed using RNA isolated from myometrial tissue removed from a 50-year-old Caucasian female during a vaginal hysterectomy. Pathology indicated residual atypical complex endometrial hyperplasia. Pathology for the associated tissue removed during dilation and curettage indicated fragments of atypical complex hyperplasia and a single microscopic focus suspicious for grade 1 adenocarcinoma. Patient history included benign breast neoplasm, hypothyroid disease, polypectomy, and arthralgia. Family history included cerebrovascular disease, atherosclerotic coronary artery disease, hyperlipidemia, and chronic hepatitis.	Library was constructed using RNA isolated from lung tissue removed from the left lower lobe of a 47-year-old Caucasian male during a segmental lung resection. Pathology for the associated tumor tissue indicated a grade 4 adenocarcinoma, and the parenchyma showed calcified granuloma. Patient history included benign hypertension and chronic obstructive pulmonary disease. Family history included type II diabetes and acute myocardial infarction.	Library was constructed at Stratagene (STR937209), using RNA isolated from the skeletal muscle tissue of a patient with malignant hyperthermia.	mammoplasty. Patholo presented with hype ity, lumbago, glaucor itis, uterine cancer the liver, cerebro	Library Description

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## Table 4 (cont.)

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8 2	81	80	79	77	76		Nucleotide SEQ ID NO:
PROSNON01	BRAITUT08	BRAINOT04	HNT2RAT01	HUVELPB01	BRAUNOT01	PENCNOT01	Library
This library was constructed from 4.4 million independent clones from a prostate library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male who died from a self-inflicted gunshot wound. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization	library was constructed using RNI left frontal lobe of a 47-year-old ugeal tissue. Pathology indicated radionecrosis. Patient history la, hyperlipidemia and epilepsy. In malignant prostate neoplasm.	This library was constructed using RNA isolated from the brain tissue of a 44-year-old Caucasian male with a cerebral hemorrhage. The tissue, which contained coagulated blood, came from the choroid plexus of the right anterior temporal lobe. Family history included coronary artery disease and myocardial infarction.	This library was constructed using kNA isolated from HOV-EC-C (ATCC CRL 1/30) certs. This library was constructed at Stratagene (STR937231), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 24 hours.	library was ulated with obeen treated s, or 1 unit.	Library was constructed using RNA isolated from caudate/putamen/nucleus accumbens tissue removed from the brain of a 35-year-old Caucasian male who died from cardiac failure. Pathology indicated moderate leptomeningeal fibrosis and multiple microinfarctions of the cerebral neocortex. Patient history included dilated cardiomyopathy, congestive heart failure, cardiomegaly and an enlarged spleen and liver.	Library was constructed using RNA isolated from penis corpus cavernosum tissue removed from a 53-year-old male. Patient history included untreated penile carcinoma.	Library Description

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89 88 87	88	87	•	001	85	84	1	Nucleotide
H 0	60		<u>.</u>	ra	8	ш	.	
SINTNOT13 SINTNOT13	SINTNOT13	;INTNOT13		PROSNOT16	STOMFET01	BRAITUT13	PANCTUT01	Library
Family history included benign hypertension, acute myocardial infarction, hyperlipidemia, and arteriosclerotic coronary artery disease.  This library was constructed using RNA isolated from ileum tissue obtained from a 25-year-old Asian female during a partial colectomy and temporary ileostomy. Pathology indicated moderately active chronic ulcerative colitis, involving colonic mucosa from the distal margin to the ascending colon. Family history included hyperlipidemia, depressive disorder, malignant cervical neoplasm, viral hepatitis A, and depressive disorder was constructed using RNA isolated from ileum tissue obtained from a 25-year-old Asian female during a partial colectomy and temporary ileostomy. Pathology indicated moderately active chronic ulcerative colitis, involving colonic mucosa from the distal margin to the ascending colon. Family history included hyperlipidemia, depressive disorder, malignant cervical neoplasm, viral hepatitis A, and depressive disorder.  This library was constructed using RNA isolated from lung tissue removed from a	chenia gravis. Patient history included osteoally history included benign hypertension, acute lipidemia, and arteriosclerotic coronary artelipidemia, and arteriosclerotic coronary artelibrary was constructed using RNA isolated frold Asian female during a partial colectomy as ated moderately active chronic ulcerative collistal margin to the ascending colon. Family essive disorder, malignant cervical neoplasm, eder.  Ilibrary was constructed using RNA isolated frold Asian female during a partial colectomy as ated moderately active chronic ulcerative collistal margin to the ascending colon. Family essive disorder, malignant cervical neoplasm, eder.	chenia gravis. Patient history included osteoally history included benign hypertension, acute lipidemia, and arteriosclerotic coronary artelipidemia, and arteriosclerotic coronary artelibrary was constructed using RNA isolated frold Asian female during a partial colectomy and the description of the ascending colon. Family issive disorder, malignant cervical neoplasm, order.	rthritis and type II diabetes. myocardial infarction, ry disease.		using RNA isolated from the stomach tissue of a died at 20 weeks' gestation.	using RNA isolated from brain tumor tissue respectively. The solution of a syear-old Caucasian male during excision of a indicated a meningioma in the left frontal lob	RNA isolated from pancreatic tumor tissue rere during radical subtotal pancreatectomy. Pathocarcinoma. Patient history included type II scular disease, benign neoplasm in the large legical included a total splenectomy, cholecystectory history included cardiovascular disease, type with the control of the control of the cardiovascular disease, type with the control of the cardiovascular disease, type with the cardiovascular disease, type with the cardiovascular disease, type with the cardiovascular disease.	Library Description

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8	97	96	95	93	92	91	Nucleotide SEQ ID NO:			
AURENOTOS	NPOLNOT01	SINIUCT01	ESOGTUT02	LUNGFET05 ENDANOT01	OVARTUT01	LUNGTUT03	Library			
removed from a 43-year-old Caucasian male during nephroureterectomy, regional lymph node excision, and unilateral left adrenalectomy. Pathology for the associated tumor tissue indicated a grade 2 renal cell carcinoma mass in the posterior lower pole of		library was constructed using RNA isolated from from tissue obtained from one of the constructed using RNA isolated from the constructed of the constructed during a total intra-abdominal colectomy and endoscopic nostomy. Previous surgeries included polypectomy, colonoscopy, and spinal canaparation. Family history included cerebrovascular disease, benign hypertension, rosclerotic coronary artery disease, and type II diabetes.	library was constructed using RNA isolated from esophageat cumor cissue on a 61-year-old Caucasian male during a partial esophagectomy, proximal ectomy, pyloromyotomy, and regional lymph node excision. Pathology indicate live grade 3 adenocarcinoma in the esophagus. Family history included cosclerotic coronary artery disease, type II diabetes, chronic liver disease ary cardiomyopathy, benign hypertension, and cerebrovascular disease.		library was constructed using RNA a 43-year-old Caucasian female dur les. Pathology indicated grade 2 mu ovary. Patient history included mititis. Family history included athereatic cancer, stress reaction, cerine cancer.	This library was constructed using RNA isolated from lung tumor tissue removed from the left lower lobe of a 69-year-old Caucasian male during segmental lung resection. Pathology indicated residual grade 3 invasive squamous cell carcinoma. Patient history included acute myocardial infarction, prostatic hyperplasia, malignant skin neoplasm, and tobacco use.				

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## Table 4 (cont.)

Т			70			101	10 11
106	105	104	102	101	100		Nucleotide SEQ ID NO:
つのる中につかりつ	PLACFER01	COLHTUT01	PLACNOT05 HELATXT03	BRADDIT02	LUNGNON03	BRAIUNT01	Library
whic library was constructed using RNA isolated from a treated, transformed embryonal	library was constructed using RNA isolated from placental dissian fetus who died after 16 weeks' gestation from fetal discephalus. Serology was positive for CMV antibody.	This library was constructed using RNA isolated from colon tumor tissue removed from the hepatic flexure of a 55- year-old Caucasian male during right hemicolectomy, incidental appendectomy, and permanent colostomy. Pathology indicated invasive grade adenocarcinoma. Patient history included benign hypertension, anxiety, abnormal blood chemistry, blepharitis, heart block, osteoporosis, acne, and hyperplasia of prostate. Family history included prostate cancer, acute myocardial infarction, stroke, and atherosclerotic coronary artery disease.		using RNA isolated from diseased choroid plexus tissue ved from the brain of a 57-year-old Caucasian male, wh ccident. Patient history included Huntington's disease	library was constructed from 2.56 x 1e6 independent clones from a lung tary. RNA was made from lung tissue removed from the left lobe a 58-year-casian male during a segmental lung resection. Pathology for the associate indicated a metastatic grade 3 (of 4) osteosarcoma. Patient history in tissue cancer, secondary cancer of the lung, prostate cancer, and an actenal ulcer with hemorrhage. Patient also received radiation therapy to the operitoneum. Family history included prostate cancer, breast cancer, and emia. The normalization and hybridization conditions were adapted from ScepNAS (1994) 91:9228; Swaroop et al., NAR (1991) 19:1954; and Bonaldo et me Research (1996) 6:791.	This library was constructed using RNA isolated from SK-N-MC, a neuroepithelioma cell line (ATCC HTB-10) derived from a 14-year-old Caucasian female with neuroepithelioma, with metastasis to the supra-orbital area.	Library Description

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Table 4 (cont.)

Nucleotide   Library	Library	Library Description
SEQ ID NO:		
107	BRAENOT02	This library was constructed using RNA isolated from posterior parietal cortex tissue
		removed from the brain of a 35-year-old Caucasian male.
108	FTUBTUT02	This library was constructed using RNA isolated from fallopian tube tumor tissue
		removed from an 85-year-old Caucasian female during bilateral salpingo-oophorectomy
	1	and hysterectomy. Pathology indicated poorly differentiated mixed endometrioid and
		serous adenocarcinoma confined to the mucosa without mural involvement. Endometrioid
		carcinoma in situ was also present. Pathology for the associated uterus tumor
		indicated focal endometrioid adenocarcinoma in situ and moderately differentiated
		invasive adenocarcinoma in an endometrial polyp. Metastatic endometrioid and serous
		adenocarcinoma were present. The patient presented with a pelvic mass and ascites.
		Patient history included medullary carcinoma of the thyroid and myocardial
		infarction.



## able 5

HMMER	BLIMPS	FASTA	BLAST	ABI AutoAssembler	ABI/PARACEL FDF	Program ABI FACTURA
An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	A program that assembles nucleic acid sequences.	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Description  A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.
Krogh, A. et al. (1994) J. Mol. Biol. 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.	PE Biosystems, Foster City, CA.	PE Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Reference PE Biosystems, Foster City, CA.
Score=10-50 bits for PFAM hits, depending on individual protein families	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less		Mismatch <50%	Parameter Threshold

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## [able 5 (cont.)

Motifs	SPScan	Consed	Phrap	Phred	ProfileScan	Program
A program that searches amino acid sequences for patterns that matched those defined in Prosite.	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	A graphical tool for viewing and editing Phrap assemblies.	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Description
Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Reference
	Score=3.5 or greater		Score= 120 or greater; Match length= 56 or greater		Normalized quality score > GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.	Parameter Threshold

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1. An isolated polypeptide comprising an amino acid sequence selected from the group

consisting of:

SEQ ID NO:53, and SEQ ID NO:54,

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- a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:3, SEQ ID
- amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:23, SEQ ID NO:33, SE

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an

and SEQ ID NO:34, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:44, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:45, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:45, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:45, SEQ ID NO:48, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:45, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:48

SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:36, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:44, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SE

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:17, SEQ ID NO:17, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:18, SEQ ID NO:15, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:

NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, and SEQ ID NO:54, and

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MO:34, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:30, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:36, SEQ ID NO

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID

3. An isolated polynucleotide encoding a polypeptide of claim 1.

NO:51, SEQ ID NO:52, SEQ ID NO:53, and SEQ ID NO:54.

- 4. An isolated polynucleotide encoding a polypeptide of claim 2.
- 5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID
- 6. A recombinant polynucleotide comprising a promoter sequence operably linked to a

polynucleotide of claim 3.

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- 7. A cell transformed with a recombinant polynucleotide of claim 6.
- 8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

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11410/10 OM PCT/US00/19948

9. A method for producing a polypeptide of claim 1, the method comprising:

comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said

- b) recovering the polypeptide so expressed.
- 10. An isolated antibody which specifically binds to a polypeptide of claim 1.
- 11. An isolated polynucleotide comprising a polynucleotide sequence selected from the 01
- ID NO:106, SEQ ID NO:107, and SEQ ID NO:108, NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:105, SEQ NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID MO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID SI NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55, SEQ ID group consisting of:
- NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, MO:93' 2EG ID NO:95' 2EG ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID MO:81' 2EG ID NO:88' 2EG ID NO:89' 2EG ID NO:90' 2EG ID NO:91' 2EG ID NO:95' 2EG ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID MO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID 52 MO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:71, SEQ ID ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:64, SEQ ID polynucleotide sequence selected from the group consisting of SEQ ID NO:55, SEQ ID NO:56, SEQ b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a
- c) a polynucleotide sequence complementary to a), SEQ ID NO:107, and SEQ ID NO:108, 30
- d) a polynucleotide sequence complementary to b), and
- e) an RMA equivalent of a)-d).
- 12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a 32

polynucleotide of claim 11.

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claim 1, and

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13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

- a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides
- comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and, optionally, if
- .

  14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.
- 15. A method for detecting a target polynucleotide in a sample, said target polynucleotide
- having a sequence of a polynucleotide of claim 11, the method comprising:

  a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction
- amplification, and

  b) detecting the presence or absence of said amplified target polynucleotide or fragment
- 16. A composition comprising an effective amount of a polypeptide of claim 1 and a
- 20 pharmaceutically acceptable excipient.

thereof, and, optionally, if present, the amount thereof.

present, the amount thereof.

- 17. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:33, SEQ ID NO:33, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:33, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SE
- 18. A method for treating a disease or condition associated with decreased expression of functional CCYPR, comprising administering to a patient in need of such treatment the composition of claim 16.
- 19. A method for screening a compound for effectiveness as an agonist of a polypeptide of

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claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

- b) detecting agonist activity in the sample.
- ς 20. A composition comprising an agonist compound identified by a method of claim 19 and
- a pharmaceutically acceptable excipient.

and

32

- 21. A method for treating a disease or condition associated with decreased expression of
- claim 20. 01 functional CCYPR, comprising administering to a patient in need of such treatment a composition of
- of claim 1, the method comprising: 22. A method for screening a compound for effectiveness as an antagonist of a polypeptide
- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample. SI
- and a pharmaceutically acceptable excipient.

23. A composition comprising an antagonist compound identified by a method of claim 22

- CCYPR, comprising administering to a patient in need of such treatment a composition of claim 23. 24. A method for treating a disease or condition associated with overexpression of functional 70
- 52 I, said method comprising the steps of:
- conditions, and a) combining the polypeptide of claim 1 with at least one test compound under suitable
- a compound that specifically binds to the polypeptide of claim 1. b) detecting binding of the polypeptide of claim I to the test compound, thereby identifying

25. A method of screening for a compound that specifically binds to the polypeptide of claim

- 26. A method of screening for a compound that modulates the activity of the polypeptide of 30
- a) combining the polypeptide of claim I with at least one test compound under conditions claim 1, said method comprising:
- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, permissive for the activity of the polypeptide of claim 1,
- c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound

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compound that modulates the activity of the polypeptide of claim 1. in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change

- :gnising: polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method 27. A method for screening a compound for effectiveness in altering expression of a target ς
- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.
- 28. A method for assessing toxicity of a test compound, said method comprising:
- a) treating a biological sample containing nucleic acids with the test compound;
- b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at
- sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim hybridization complex is formed between said probe and a target polynucleotide in the biological SI least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific
- c) quantifying the amount of hybridization complex; and 11 or fragment thereof;

50

- d) comparing the amount of hybridization complex in the treated biological sample with the
- compound. amount of hybridization complex in the treated biological sample is indicative of toxicity of the test amount of hybridization complex in an untreated biological sample, wherein a difference in the

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Cys Ala Gln Lys Cys Ala Phe Asn Asp Thr Arg Glu Glu Gly
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225
Ala Gln Tyr Tyr Phe Lys Cys Lys Leu Trp Asp Glu Ala Ser Thr
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OTS
Clu ile Val Glu His Leu Glu Glu Ser Thr Ala Phe Arg Tyr Leu
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522
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yla Wet Leu Pro Pro Asn Val Ile Asp Thr Asp Phe Ile Asp Glu
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OTZ
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Ser Gly Ser Gly Asn Met Pro Ala Ser Val Ala His Val Pro Ala
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Ser Ser Ser Gly Gly Gly Ala Gly Ser Ser Asn Ser Gly Gly Gly
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SOL
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GJU His bhe Arg Asp Cys Asn Pro Lys His Ser Gly Gly Ser Ser
OST
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Pro Asp Leu His Pro Ala Ala Gly His Gln Met Asn Gly Thr Asn
SET
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Asn Gln Tyr Phe Asn His His Pro Tyr Pro His Asn His Tyr Met
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Glu Gly Ger Leu Pro Ala Ser Met Gln Leu Gln Lys Leu Asn
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yja ykd bhe Asn Asn Ser Gin Phe Met Gly Pro Pro Val Ala Ser
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rks yrd yrd gju gju rks gjn bro ren ije lkr gjn ser ysb yrd
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Pro Pro Lys Ala Arg Pro Gin Met Asp Leu Ile Ser Giu Leu
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GIN WIS ASP Thr Pro GIN LUS GIN GIN Pro Pro Are Ler Lus Ser
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Gju Gjn Asi Gjn Gju Trp Lys Lys Glu Ala Ala Ala Gln Glu Ala
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SES
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GIN LAK BUG GIN GIN YEU BIO TAR LUK LUK SEK BIO GIN TEN BUG
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ren yja yab set Lys Thr Ala Gln Glu Ser Val Val
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ren ris ejn bye ren yzd yjs yzu ser bro lyr Wet yzb ris ren
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CIN AST FEN WEE SER FEN AST IJE CIN WEE CIA FEN YED YRA ITE
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ORF
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ein Arg ein Lys ein Arg ein Lys ein Lys eiu Arg eiu Lys
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ras ein arg ein Lys ein Lys ein arg ein Lys ein Lys
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yau Ser Thr Pro Leu Gly Ser Ser Lys Glu Thr Arg Lys Gln Glu
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SET
Val Thr Ala Glu Gly Leu His Pro Ser Leu Pro Ser Pro Thr Gly
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Pro Pro Val Arg Arg Ala Ser Ala Gly Pro Ala Pro Gly Pro Val
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507
Lys Ser Arg Gly Ser Arg Ala Ala Gly Gly Ala Pro Ser Pro Pro
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Pro Pro Leu Gly Pro Ser Ser Leu Leu Ser Leu Pro Gly Leu
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Leu His Gly Ser Arg Ala Ile His Glu Glu Arg Arg Gln Gln
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                    322
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Trp Arg Glu Thr Arg Gly Glu Leu Gln Tyr Arg Pro Ser Arg Arg
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Thr Glu Ala Leu Ile Glu Arg Glu Asn Ala Ala Gln Leu Lys Lys
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Met Gln Glu Asp Phe Leu Val His Glu Val Thr Asn Leu Pro Val
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SIE
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Arg His Thr Leu Gly Ser Val Glu Lys Leu Arg Ser Cys Gln Gly
SRZ
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Asp Pro Lys Trp Leu Asp Val Ile Glu Lys Asp Leu His Arg Gln
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GJu FAz Asj FAz Fen ytd CAz ytd FAz GJA IJe bto 2et 2et Fen
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ren yab wer bye zer yau 1xb yab ria 1xb ren zer yrd yrd bue
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Ser Ser Ile Pro Val Asp Val Ala Arg Gln Arg Glu Leu Lys Trp
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ris tir Gly Phe Leu Gly Gly Ser Gln Tyr Ser Gly Ser Leu Glu
                     52
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CIY Ser Asp Ser Glu Ile Asn Gly Leu Ala Leu Arg Lys Thr Asp
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                     OI
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Ytd rks ysb ren ren cji lit ren ysu cji cjn yjs set lut set
                     ςg
yrd yrd yjs yjs Lyr Gjn yau ije bro ysj yrd yrd bro yab
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                                          9
Leu Phe Leu Asn Asn Val His Leu Ser His Pro Val Tyr Val
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GIN THE GIT GIT BLO YER GIT LAK LAK LUK TEN YED SEK IJE
Set Itp Pro Lys Ash Val Lyr Ash Tyr Val Trp Gly Thr
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Agi Agi Wet Asn Ala Abr Leu Ser Tyr Cys Gin Lys Glu Ala
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bye Hiz Cys Pro Ala Asp Ser Ser Glu Leu Ala Tyr Asp Pro Pro
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Leu Gly Leu Asn Val Pro Leu Leu Phe Tyr His Phe Trp Arg Tyr
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Ser Leu Phe Cys Ile Met Phe Leu Cys Ala Gln Glu Trp Leu Thr
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yau bio yai His Ala Arg Glu Arg beu Arg Asn Ile Glu Arg Ile
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bye yab cyn ren yrd Lyr yab bye ria ger bro ije yab cyn Cya
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OIS
GJn FAz FAz YJG GJU GJA YLG FAz FGn SGL FGn YLG FAz YJG
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GIU GIN TAR GIN YLA GIN TAR GIU GIN TAR GIU YLA GIU TAR GIU
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MO 01/01/11 LT/1/200/16648

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MO 01/01/11 bCL/\(\Omega{200}\) bd48

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56Þ
yab cjn Asi yad ren yab bro yan Asi cju rya Trp Asp Val Thr
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Pro Val Asp Ile Phe Ala Lys Ile Lys Ala Phe His Leu Lys Tyr
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Ile Ile Ile 11e Pro Ala Ala Thr Thr Ser Leu Ile Thr Met Leu
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Nal Lys Ala Arg Glu Glu Gly Arg Ala Pro Glu Gln Arg Pro Ala
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GIN YIG PEN YIS YIG PEN GIN GIN HIS PAR GIN GIN IJE NSI
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Ser Thr Gln Val Lys Arg Ala Ala Asp Glu Val Leu Ala Glu Ala
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Wet Gin Leu Pro Gin Giy Gin Thr Giy Ser Val Giy Thr Ser Val
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COT
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Clu bye cin Thr Leu Asp Val Gin Thr Gin Gin Met Giu Asp Thr
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JZO
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Wet Asn Leu Glu Lys Ile Ser Ala Leu Met Asp Lys Phe Glu His
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SOT
SET MET ALA GLY VAL LYS SET MET ASP ALA THE LEU LYS THE
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YIS ALG VAL GIN THY ALA VAL THY MET GLY LYS VAL THY LYS
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CJU VJS VZJ AST PRE LEU Arg Met Ser Ala Arg Asp Ala Val
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Glu Val Ala Arg Ile His Ala Glu Asn Ala Ile Arg Gln Lys Asn
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Ser Ser Lys Ala Leu Val Lys Met Gln Leu Leu Lys Asp Val Val
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MO 01/01/11 LT/US00/19948

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Trp Ala Gly Ser Gln Ser Arg Arg Leu Gln Arg Arg Leu Thr Glu
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56T
Thr Pro Asp ile Leu Gin Pro Gly Gly Thr Phe Leu Cys Lys Thr
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Wap His Asp Arg Leu Ile Ser Leu Cys Leu Thr Leu Leu Ser Val
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OZT
GIY Phe Val Leu GIY Val Asp Leu Leu His Ile Phe Pro Leu Glu
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 Cys Phe Ala Val Ile Val Ser Ala Lys Arg Ala Val Glu Arg His
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08	3₹	nar	חבת	ĀΤĐ	HSA	SLF	qsA	BIA	JUJ.	ďs4	0.∠₹ 100	әтт	rλa	сЛа	эті
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יז	БV	<b>D</b> LO	zəs	сŢл	Val		гел	IJG	ΊΛŢ	еји		zez	siH	ько	CŢn
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C	C F					930					452				
		ΓGπ	ελη	ΛgJ	дуL		СŢIJ	pxA	ько	ςζη		ДуL	IJe	qsA	CVS
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		дух	ľys	сŢХ	zəs	355 gsA	гĀз	asA	nŢĐ	siH	350	ալց	2 iH	ſεV	> h
S	36 36	сτλ	ΤΛτ	сЛз	ьре	GJn	Τ <u>Υ</u> τ	гЛз	Trd	TYD		Val	сух	вуλ	YXd
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	ya EE	SYD	TVT	zes	GJ^	35E	nəŋ	અપૃત	ແເຍ	2V.I	320	rre-I	սլց	asy	CLD (
J	цL	nəŋ	rλa	zəs	IJe	siH	дŲД	дуд	стх	Val	дуд	กอๆ	Val	Pro	eŢu
9	33	<i>[</i> = 0		<b>~</b> 711	241	370	гλз	CTU	at T	pT¥	305	ಎಬ್	D.I.A	กรอ	กรอ
Λ	n۶					567					062				
s	ΓX	дух	zəs	egu	пәп		eŢn	сŢл	syJ	nsA		βXĄ	ьре	bro	LsV
5	28	חבת	277	nto	חדם	780 780	นาจ	กรอ	กอา	นาอ	S7S	กอา	дуд	пәŢ	ько
Λ	17					597					760				
		ьуе	Pro	zəs	сŢХ		пәт	zəs	eŢu	SYS	ъре S₹2		gsA	nsA	IsV
2	52 52	261	AIA	PLG	әиа	320 V.	ΤΥΥ	гЛз	Pro	sīH			nəŋ	nəq	bro
Λ	57					235					230				
	-	req	IJe	[sV	Val	SS0	TVT	СЈп	SVD	дŲД	TPX SIS		ເເເຍ	ςſΑ	LaV
z	75 26:	nəŋ	IJe	ejn	siH	ΓΛε	zəs	ејп	ько	siH			Tyr	Met	Λsl
٨	T7					502					200				
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U	isA ior	ејλ	дәм	стх	Val	Pro	TYT	τχr	ько	дух			еух	eJn	all
0	18	a Far	****	077	277	571 275		TEC	e Yu	กรจ	710 178		פדת	BLA	gjn
c	тο					09T					SST				
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C	120	<b>T X T</b>	חדה	STU	att	S#I	тте	s⊼π	ure	Хτэ	ITO LUL		sĀŋ	פות	gŢπ
-	CT					130					571				
5	ΗŢ	TYr	gJn	yrd ,	IJ6			сŢХ	SIH	CYs	110 Val	. nte	I <sub>Y</sub> r (	, лул	q1T
(	Т5( .т.Х.т.	261	กรอ	этт	PIA	II2 <sub>I</sub> Xx	Zer	sλɔ	zəs	zes			ьуе з	ุ กอๆ	<b>b</b> ko
	:nT					001	•				96				
		nəŢ	пэд	nte	Arg (		us4	oxa	зуХ	s VJ	80 []\t	' asA	y sag	[ n[5	eJn (
(	)6 วาก	กรอ	₫s₩	. KTE	zəs	82 Lyk:	' Lsv	ุกอๆ	oza	ູ nəŋ	[]e	sλ	sλī	[XX]	. sVJ
	= /					07.					59				
		s <u>Y</u> d	siH	s1A	I.J.	, лц <u>л</u> 22	, дәм	IJG	[ LEV	[VK	usy 20	ast	ניון ב	יא אי	TYr
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(	30					70					30				

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Ser Ser Thr Pro Ser Pro Ser Leu Asn Leu Gly Asn Thr Glu Glu
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                                         5₹2
gru gru bio lur arg pro Gln Gln Ser Thr Gly asp Thr Met
5₫0
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                                         230
bro Glu Ala Glu Ala Glu Asa Leu Pro Asp Asp Lys Pro
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LPL BUG CGN GJN FGN TAK TAK CGN GJN GJA FAS FGN FGN FUG
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                                         200
ras ein ein ala ein ein ein arg as lys leu ein arg Tyr ein
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                                         58T
LPL GJU GJU GJU F60 YSD GJA NSJ BY6 GJU FAS F60 GJA YSU F60
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                                         OLT
His Leu Ala Glu Val Ser Ala Glu Val Arg Glu Arg Lys Thr Gly
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Ala Val Gln Asn Gln Trp Gln Leu Gln Gln Lys His Leu Gln
OST
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                                         OPT
Gin Gin Leu Gin Ala Lys Lys Gin Met Ala Met Giu Lys Arg Arg
32T
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                                         T52
Wet Glu Glu Ala Gln Arg Lys Arg Thr Gln Leu Arg Glu Ala Phe
150
                    SII
                                         OIT
His Val Glu Ala Ile Lys Ile Gly Leu Thr Lys Ala Leu Thr Gln
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                                         S6
yjs yjs råz gjn gju 1xb råz gjn ren råz yjs 1, 1, 1, x yzd gjn
06
                    58
                                         08
ren yab bio leu Ala Ser Glu Asp Thr Ser Arg Gln Lys Ala Ile
SL
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Yab bye ren gju yau ije ren yja gju gjn yab lyr yja rka gjk
09
Set GJU FAS FAS YSD FAS FEN CHS SEK GJU FEN GJU AST YJS
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SĐ
Clu Ala Glu Leu Pro Ala Lys Ile Leu Val Glu Phe Val Val Asp
                    52
                                         0.2
ren yla Gin Val Ala Giy Ile Leu Giu Pro Val Giy Leu Gin Giu
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PCT/US00/19948

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MO 01/01/11 FCL/0/200/19948

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GJU FÅR AST YKA LÅK GJA SEK LÅK YJS FEN LUK SEK GJN GJN
                    385
                                         380
390
Ile Val Glu Asp Glu Glu Glu Ser Val Ala Leu Glu Gln Ala
                                         392
948
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SET ATG GLY SET ASD SET GLY MET ASP SET ASD LE ASP LEU TAT
390
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                                         320
ren Asi Gin Giy Giu ile Ala Giu Giu Ala Ala Giu Lys Ala Thr
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                                         332
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GIN SEr Phe Ala Glu Gly His Ser Glu Ala Ser Leu Ala Ser Ala
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                                         350
GJn yab ren bro ser ser Glu Gln Met Pro Asn Asp Gln Glu Glu
STE
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                                         305
rks ast arg clu cly clu ser His ala Glu asn clu Thr Lys Ser
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                    562
                                         062
Lys Ser Ser Pro Phe Lys Val Ser Pro Leu Thr Phe Gly Arg Lys
285
                                         SLZ
IJG FAS PAS SER FGN LPR SER WSU HIS GJU FAS IJG SER SER GJA
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YEN INE LEU GIY Thr LYS Ile Val Ser Val Glu Arg Glu Lys
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Ser Leu Lys Lys Ala Phe Ser Arg Gln Asn Ile Glu Lys Lys Met
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                                         230
Ser Arg Ala Glu Lys Ile Lys Arg Ser Ser Leu Lys Lys Val Asp
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yab ejn ejn yis ren ejn yab aer yis ejn ejn rka Asj ejn ejn
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                                         200
SIO
Thr Leu His Thr Val Asp Leu Ser Ser Asp Asp Asp Leu Pro His
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56T
                    06T
GIN GIY LYS GIN GIN Leu Pro Asp Glu Asn Lys Ser Leu Glu Glu
                    SLT
                                         OLT
08T
IJG Dro Ala Ser Val Phe Val Lys Gln Pro Val Ser Gly Ala Val
SPT
                    09T
                                         SST
yrd yrd ysu His bye FAs Asl Fen Ile bye Glu Glu Glu ysu Glu
OST
                    STT
                                         OPT
Cys Ala Gln Val Lys Arg Leu Glu Asn Asn His Ala Gln Leu Leu
                    T30
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SET
Val ser Ala His Thr Arg Ala Val Lys Glu Arg Met Asp Arg Gln
OZT
                    STT
                                         OTT
Ser Thr Ser Asn Thr Val Ser Lys Leu Leu Glu Lys Ser Arg Lys
SOT
                    00T
rks cjk ije cju yau yab ren lyr rks ren ser rks lyr cju yjs
06
                    28
CJW Hiz rvs Met Glu Glm Arg Glm Ile Ser Leu Glu Gly Ser Val
ren ren yab ria ren ial yau wet ren yab ala val Glu Glu Asn
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                                         ٥٥
yla ile Arg Asp Asn Ser Gin Val Asn Ala Val Thr Val Leu Thr
SĐ
                                         32
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18/63

<400> 22

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yjs ren yjs vis rka ser ren yjs yrd yrd yrd yrd yrd yrd
                    SS
Gin Gin Giy Ala Ala Giu Pro Ala Lhr Arg Lys Arg
                                        32
LPR WIS SER GIN GIN WED PRO GIN GIN PEN GIN WIS GIN WED
                                        07
GIN GIN GIN TAR WED GIN GIN HIR WED GIN GIN LUL WED BY DEO
WEE LEU GIN Thr Pro Glu Ser Arg Gly Leu Pro Val Pro Gln Ala
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SOI
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ren yau yab LAx yxd CJA bye ren yJs CJn Wet rAs Axd Asl bye
                    58
                                        08
yla Leu Gin Trp Val ile Pro Tyr ile Lys Lys Glu Ser Pro Leu
                                        9
yab yis ren rys Val Thr Phe Leu Ile Thr Arg Leu Thr Gly Pro
                                        05
                    55
GIN THY GIY SET TYT MET PRE VAL ASP GIU ASR THY PRE SET SET
GIN Thr Phe Asp GLY Asp Thr Asp Arg Leu Pro Glu Phe 11e Val
                    97
                                        0.7
IJG YKA BLO YJY LYK YKA YKA LKD YKA YEU BLO IJG BKO BKO
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ISO
                                        OTT
                    SIL
His Ser Leu Arg Ala Val Ser Thr Asp Pro Pro His His Asp His
                    OOT
                                        96
GIN ASI YLA GIU PEN WEL GIN PAR PEN YLA GIN PAR GIU PEN SEL
bro Glu yla Arg Met Arg Glu Glu Asn Met Glu Arg Ile Gly Glu
Pro 11e Leu Gln Tyr Arg Trp Asp 11e Met His Arg Leu Gly Glu
                    \varsigma\varsigma
Tyr Cys Val Pro Arg Gly Asn Arg Arg Pre Arg Val All Gln
                    0Ŧ
                                        32
yla Asn Lys Gly Glu Pro Leu Ala Leu Pro Leu Asn Val Ser Glu
                                        20
                    52
yau Aal Asn Gln Glu Asn Asp Glu Lys Asp Glu Lys Glu Gln Val
ST
                    OT
WET GIN SET LYS GIN GIN ATG Ala Leu Asn Leu Ile Val Glu
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OST
                    STT
                                        OPT
Cys Tyr Ser Asn Gln Ser Asp Asp Gly Ser Asp Thr Glu Met Ala
332
                    J30
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Asp Ala His Ser Thr Thr Ser Ser Ala Ser Pro Ala Gln Ser Pro
                                         OIL
ISO
                    STT
YZU CJU IJG ZGL PAZ PGN CJU PAZ CJN byG PAZ YLG HIZ YZU ZGL
                    TOO
                                         96
SOL
TAS BIO FAS TAS ASI FAS TAT LEU SET GLY ASD AIG LIE LYS SET
06
                    58
His Val Val Asp Ala Arg Ala Gly Pro Ser Leu Lys Thr Leu
                                         59
                    04
rys Arg Trp Lys Lys Leu Pro Ala Gly Ser Lys Lys Asn Trp Asn
                    55
                                         05
GIN THY AYG SET GIY ASP Ile Cys Ash Ala Val Leu Leu Val
                                         32
                    ΟĐ
Ser Lys Arg Tyr Glu Lys Asp Phe Gln Ser Cys Phe Gly Leu His
                    52
                                         20
CAS CAS IJG CAS YLA YJY PAS SGL SGL SGL YLA LYL YSD
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Arg Ala Lys Ala Arg Ala Glu Ala Ser Met Arg Ala Arg Ala Ser
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bro Val Gln Tyr Arg Glu Ala Leu Ala Asp Glu Ala Arg Ala
                    592
                                         092
07.7.
ren gjy phe val Ala Lys Leu His Lys Cys Glu Pro Gln His Trp
552
                    220
                                         S$2
Ser Trp Gly Pro Arg Ser Asn Leu Glu Ile Ser Lys Met Glu Val
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240
                    232
Ser Tyr Arg Arg Val Pro His Thr Asn Pro Pro Ala Tyr Glu Phe
                    220
                                         512
522
bro Lys Arg Leu Ile Met Glu Asp Phe Val Gln Gln Arg Tyr Leu
                    202
                                         200
Ytd ren cly Val Gln Pro Ser Lys Tyr His Phe Leu Phe Gly Tyr
                    06T
                                         58T
yxd cjl yzu zer yjs yxd cjn yjs cju nsj trp cju Met Leu Arg
                                         0/.T
08T
                    S/.T
Pro Arg Leu Gly Leu Leu Met Met Ile Leu Gly Leu Ile Tyr Met
                                         SST
59T
bro Leu Glu Glu Glu Glu Glu Glu Asp Leu Gly Gly Asp Gly
                                         OPT
                    STT
OST
bye yab yad ria Hia Hia Lyr Lyr Ile Leu Ile Asn Lys Leu Lys
                    T30
                                         125
SET
YIS ALE GLU His Leu Arg Tyr Val Phe Gly Phe Glu Leu Lys Gln
                    STT
                                         OTT
TSO
Λ<sup>g</sup>J IJG GJλ Y2D ΓGn Γλ2 IJG ΓG LTG LTG Y1g Yxἀ
                    T00
                                         56
Yap Lys Lys Lys Ser Pro Ile Thr Arg Ser Glu Met Val Lys Tyr
                    82
                                         08
ren yau yad aya elu ren val eln ren val eln phe ren val Lys
                    04
SL
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Ala Gln Phe Pro Ser Thr Ser Gly Ger Gly Tyr Lys Asn Asn
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                                        305
bro Gju yab Gjn Agj ren Agj ije yab ger bro Hiz yau ger yrd
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bro ren bro zer Irb CJA VJ9 bro bro ren yrd ysb yrd yj9 yrd
                    087
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Asp Asp Ser Asp Glu Asp Val Ile Leu Val Glu Ser Gln Asp Pro
                    592
                                        097
Ile Gly Ser Ala Asp Cys Asn Val Ile Glu Ile Asp Asp Thr Leu
                    720
                                        S72
522
Arg Ala Val Ser Pro Val Ala Phe Gin Gly Ser Pro Pro Ile Val
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                    232
077
bye ije rks yrd rks yrd bro rks yrd ser ejn ser wer val elu
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                    220
Ciu Leu lle Arg Met Val Arg Glu Glu Asp Trp Asp Asp Ala
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                                         200
OTZ
ren yrd Wet Tyr Ala Asn Glu Glu Arg Leu Pro Asn Phe Leu
                                         58T
SGT
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GIA GIA CIN ren zer yrd ysb ren yrd ren yrd ren rha ysb bye
180
                    SLT
                                         OLT
Ala Glu Lys Asp Ala Asn Arg Thr Arg Leu Gln Gln Leu Leu Leu
                    09T
                                         SST
SPT
Arg Leu Glu Val Gln Leu Gln Asn Ala Ile Gln Ala Gly Ile Ile
                                         OPT
                    STT
OST
Yen Thr Leu Gln Ala Gln Gly Glu Lys Ala Ser Leu Tyr Val Ile
SET
                    J30
                                         SZI
Phe Gly Glu Ser Glu Ser Ser Val Thr Ala His Gly Lys Phe Phe
                                         OII
150
                    SII
Pro Asn Leu Ser Val Ala Asp Phe Leu Arg Ala Met Lys Leu Val
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                                         96
SOT
Arg Gly Pro Ala Arg Glu Val Met Arg Val Leu Gln Ala Thr Asn
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                                         08
Yan Wet Ser Glu Glu Glu Lys Leu Lys Arg Leu Met Lys Thr Leu
                                         9
                    0L
Phe Glu Asn Trp Leu Thr Gln Val Asn Gly Val Leu Pro Asp Trp
                    SS
                                         05
Lys Leu Phe Ser Gly Arg Val Val Pro Ala Gln Gly Glu Glu Thr
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                                         32
SΦ
Arg Ser Leu Gly Pro Ile Met Ala Ser Met Ala Asp Arg Asn Met
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Yrd bye GJA GJn Asl ren 11e ysp Thr His Leu Phe Lys Pro Cys
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                                         OLT
081
LAL LLD PAS WIG GJU PAS 116 CAS CAS GJA 116 176 LAL PAS GJA
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59T
                    09T
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Ser Gly Ser Asn Arg Thr Pro Val Phe Ser Phe Leu Asp Leu Thr

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## 25/93

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152
321
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GJu r\s yrd Zer Gfy Leu Gln Ser Gly His Ser Ger Gln Arg
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Ser Lys Trp Thr Pro Val Gly Pro Ala Pro Ser Thr Ser Gln Ser
                    TOO
SOT
Asn Pro Asn Phe Phe Glu Gln Arg His Gly Gly Ser His Gln Ser
                                         08
                    92
Ala 11e Pro Lys Pro Thr Val Pro Pro Ser Ala Asp Glu Lys Ser
                                         9
                    01.
Clu Met Lys Asp Phe Ile Cly Asp Arg Ser Ile Pro Lys Leu Val
                                         ٥5
                    55
09
Asp Lys Leu Ser Ser Arg Ile Gln Ser Met Leu Gly Asn Tyr Asp
                    ОÐ
                                         32
Ser Ser Pro Leu Phe Ala Glu Pro Tyr Lys Val Thr Ser Lys Glu
                                         20
                    52
yrd yrd ysu gju gjn lje gju gju gjn ysb ylg bro bro
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Wer yen yad gjn yeb yad yen Asi Leu Arg Met Lys Glu Arg Glu
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Tyr Lys Leu Lys Ser Arg Gly Asn Thr Lys Met Ser 1le His Leu
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SĐ
Pro Val Gly Ile Ala Gly Phe Ala Ala Ile Val Ala Tyr Gly Leu
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375
yab yau cjn zer yab rha yjs cju nsj bye cjn yau ren ije ije
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196
yrd Cys Ser Tyr Cys Gly Glu Glu His Ser Lys Glu Thr Cys
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ren iar ben bro ihr irp ser ala gia irp iar bro beu giu gia
                    04
                                        9
GJA YSD bye YJY LLD GJN YLG AYJ YLG GJA ren GJA ren bro rAz
                    92
                                        20
Yrd Gjn Yrd Ltb yzu bye yzb bye Ayj Lyr Gjn Lyr bro ren Gjn
                    ОÐ
                                        32
Ser Arg Asp Cys Asp Ala Leu Met Ala Gly Cys Ile Gln Glu Ala
                    52
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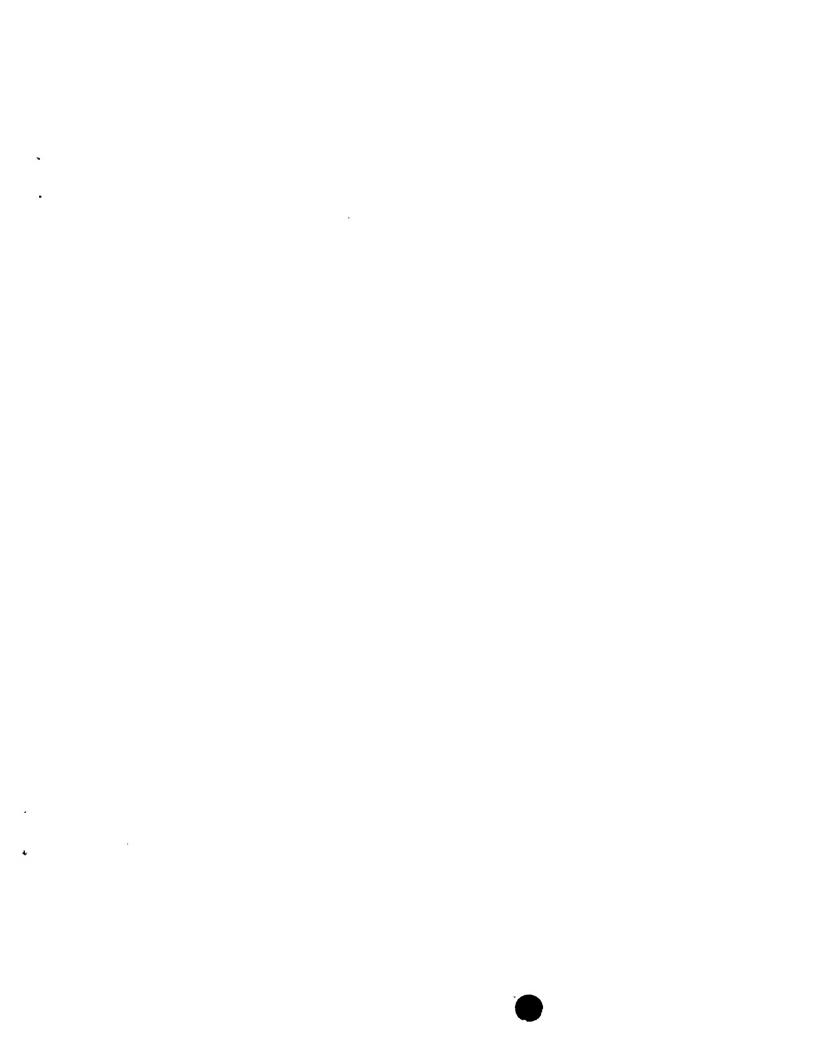
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SOT
                    TOO
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09
                    99
                                        05
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26x 26x	Γλε	rys	Lλτ	zer		Дух	zes	сух	sţH		гел	ько	ејп	дух
900 Pro	IJG	ько	đsų	Val	7AT 655	IJĢ	zez	сŢп	суп		ејп	ети	zes	суу
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322 CJX	zəs	siH	эца	nəq	097 nəŋ	bro :	nŢs	s.K.J	cys :		ողք	) nTe	rīs (	nəq
340 261 352	sIA	us4	ser.	zer	377 377 370	yrd (	. slA	. sIA	լ Ալը	215 Ala 052	377	, s <i>K</i> j	ds₩	qsA

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Ast Leu Pro Arg Glu Ile Asp Leu Asn Giu Trp Leu Ala Ser Asn
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\operatorname{Gl} n CAs \operatorname{ren} yau yab ije \operatorname{rAs} yau \operatorname{ren} bye yig \operatorname{sex} \operatorname{rAs} \operatorname{Clu}
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592

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510

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The ren Asl Thr Asp Glu Asp Val Phe Pro Thr Lys Tyr Gly Arg
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ren Ipr Ile Thr Gly Ala Gly Leu Gln Asp Leu Val Ser Ala Cys
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OTS
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MO 01/01/11 FCL/Ω200/16648

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320

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Yrd riz Ser His rig Ile Pro Lys Leu Glu Glu Glu Gln Gln Asn
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TWS Arg Lys Lys Ser Asn Lys His Asp Ser Ser Arg Ser Glu Glu
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SSI
Gln Ala Ser Glu His Thr Lys Ser Lys His Glu Ser Arg Lys Glu
180
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GIN PEN bye GIN ZER ZER PEN C'AZ GI'A YZD PEN PEN YZU GIN NYT
                    09T
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59 T
bro Gin ile Lys Leu Lys The The The The Gin Asn Giy Arg
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ren bro ren Glu Val Arg Leu Cys Pro Asp Arg Ile Ser Leu Ile
                      061
                                            SRI
ren 11e ejn kia vai ely cys Leu elu elu Phe ely vai Lys Ile
08T
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GJU FGN IJG LUL YZD YKG LKO LKO YJY IJG CJU CJN FGN FGD
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                                            SST
                      09T
Thr Asn Leu Thr Asp Ser Cys Met Asp Leu Ala Arg Cys Cys Leu
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OST
IJG YED PGN ASI PGN YJS YJS BEL GLO JAL BYG YEU ZGL ZGL
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332
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Ala His Lys Gly Asn Pro His Tyr Arg Val Ser Tyr Glu Lys Ser
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150
                      STT
Wer wer His Cys Ser Ala Cys Ser Glu Asn Pro Pro Ala Gly Ile
SOT
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Pen Leu Cys Ser Ser Arg Leu Glu Asn Ile His Leu Ala Gly Gln
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                                            08
\mathtt{L}\mathtt{p}\mathtt{x} CAs <code>Fen</code> yab <code>Zex</code> yab <code>Yey</code> CAs <code>LAx</code> <code>Cfn</code> <code>Ife</code> <code>Bye</code> <code>Lpx</code> <code>Cfn</code> <code>Zex</code>
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Arg Thr Leu Leu Gln Asp Met Leu Thr Met Gln Gln Asn Val Tyr
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Arg His Thr Gly Arg Lys Gln Pro Pro Val Ser Glu Ser His Trp
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95
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CJU ZEL ZEL CEN CJN YS YLA TÀR PEN WEL ASS YLA TOL
GJn FÅs His GJA FGn GJn FÅs BIO IJG SGI BUG AST FÅS YSU LUI
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597
ZGL CGR DIO AS DEO CJA CJR IJG IJG VJJ AST PKG AST PAZ
                      SPP
                                            077
057
The The Lto Leu Leu Glu Asp Asp Pro Gln Gly Ala Arg Lys Ile
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432
rks yrd 116 bro bro lyr rks lyr yrd bro ren yrd gyu gyk ger
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OZĐ
ras cin ala Thr Lys Lys Lys Lys Lys Cin Pae Ciy Lys Lys Arg
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Leu Gln Pro Pro Val Ala Ala Glu Pro Ala Thr Pro Leu Lys Ala
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                                            380
390
bro Asp ile Tyr Pro Val Gly Trp Cys Glu Leu Thr Gly Tyr Gln
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                                            365
312
YED GIV TTP ASP SET GIU TYF ASP GIN TTP VAI ASP CYS GIU SEL
390
                      322
                                            320
Ala Thr Val Lys Arg Val Val His Arg Leu Leu Ser Ile His Phe
                      340
                                            332
345
Lys Leu Glu Ala Val Asp Leu Met Glu Pro Arg Leu Ile Cys Val
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                                            350
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MO 01/01/11 bCL/\(\Omega \)200/16948

310

STE

Ten bye yau Wet yab Cys Pro Asn His Gly Phe Lys Val Gly Met

305

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MO 01/01/11 bCL/\(\Omega{1}\)

S <i>L</i> 9					049					S99		_	~	
ду. 099	әұа	nəŋ	ьре	еуп	nəq SS9	siH	Thr	Met	ьре	059 Val	GJn	grT	Arg	zes
	zəs	τ <u>γ</u> τ	yrd	суи	640 Ala	пәп	Ser	IJG	ьſА		zez	ŢΛτ	Val	zes
	ejn	пәд	дуд	сŢл		Γeπ	еуλ	reg	IJe		сŢл	yxd	гуs	TYr
	qsA	ąsĄ	εſΑ	Lyk		Arg	еји	Val	qsA		еух	rās	¥χα	nəq
СŢЛ	сJи	гел	IJG	цŢЭ	sIA	сյи	дуц	ьре	qsA	Гел	пәп	Arg	eŢπ	nsA
	ςλε	siH	ren	стр		дуд	гел	Zer	IJG		qsA	ејп	ько	Trd
-	стп	siH	сτη	siH		дуц	Val	siH	¥κα	-	Val	Met	ςλη	ıje
	сŢп	гуз	Бко	đsų	_	yrd	TYT	Γeπ	ько		суѕ	гХз	qsA	Arg
	ςλa	bro	ьſА	геп		ьlА	μλι	IJę	суи		zəs	Τλτ	TYT	τλτ
_	sIA	гел	eŢIJ	req		гел	slA	zəs	ько		еји	rXa	ејп	<b>ә</b> पुत
	yxa	nsA	sIA	qsA		Val	цĮЭ	bro	пәп	-	пәп	$\Gamma$ e $\sigma$	τλτ	ьlА
	ьſА	гел	дуд	Met		nsA	ько	пәд	ьlА		zəs	sIA	гел	еJп
	пәт	Val	суп	Thr		ько	ьуе	Val	сјп		Γλε	nsA	rys	sla
	ьſА	геп	syJ	GJA		Arg	гeл	гел	Val		slA	ьре	zəs	αŢĐ
	ько	Val	siH	сји		дуд	<b>ąs</b> A	TYr	дуд		ејп	zəs	дγл	ьſА
_	ьре	<b>b</b> xo	nsA	zəs		Val	zəs	ејп	Ţλι		ько	sţH	суз	етл
-	гЛз	ејп	ren	qsA		nsA	ьſА	дуд	дуд	_	IJG	сŢи	Ţλι	slA
₹50 С7λ	сух	суѕ	rλs	сти	₹I2 CJλ	сти	гел	Бко	yrd		TYr	дуд	гел	zes
₹0₽ ₹0₽	ςλη	<b>T</b> T	ДЛ	сŢIJ	₹00 СŢλ	dsy	zes	Val	ьlА	395 GJ <sub>II</sub>	nəq	Val	slA	rλa
390 390	Thr	лфТ	дуд	дуд	naA 285	zes	Гел	ſsV	гλа	380 380	дуд	түт	ьĺА	дуд
375 375	ФЛ	Arg	nəŋ	nəq	gaA 370	slA	zer	nsA	zəs	3 e z G J N	ько	Val	сγλ	Val
390 GJn	qsA	ејп	egu	LaV	sIA 225	rλε	zes	дук	nəq	320 510	zəs	slA	zəs	IJG
naA 345	nŢĐ	ејλ	сτλ	αŢŋ	siH 340	siH	all	сŢи	ьре	naA 335	IsV	yra	ети	Ιλι
330 ren	IJG	сζη	дуд	цŢэ	352 <b>r</b> en	zəs	zez	zəs	ьſА	ala 320	ren	гел	гел	ејп
312 116	zəs	Ser	ько	Pro	370 CXa	siH	лул	пәŢ	БĺА	302 Буе	slA	Met	nəŢ	ејп
300 GJu	yzd	дух	ьſА	пәп	gsA 295	цĮЭ	Ţλι	сту	ejn	360 Ser	цĮэ	ејλ	гел	egu
285 Ser	ςλε	Val	qsA	ďχŢ	280 261	гλз	ько	Ιλι	сτλ	375 Thr	εÍÁ	дәж	пәq	ејп
S10 GTD	s¥2	STH	Wet	zes	81A 265	BLA	ŗλε	ιλι	₫s₩	360 H18	ьие	¥xa	пəп	F1A -
222		·	nəŋ		220	_				542				
540			БÍĀ		235		_	_		530				
552			ΓΛε		220					SIZ				
210	_		-	_	205	()	_	-		200				-

35/93

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Leu Val Leu Leu Gln Ala Trp Pro Pro Met Lys Ser Glu Tyr
                    TT32
                                        TI30
Met Glu Leu Leu Glu Ser Ser His His Glu Ala Glu Phe Gln His
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SZII
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YSD IJG YJY YSD IJG CJN YSU CJN YSU YXG LXX CXS PGN byG
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                                        TIOO
OTTT
YIG IUI CJN YJS IJG PGN PAR YJS ZGI IID BIO CJU YIG CJU ASJ
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Ser Phe His Leu Thr Glu Glu Asp Ser Lys Leu Leu Val Phe Phe
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                    SLOT
Trp Pro Val Arg Pro Arg Ile His Val Leu Gln Ile Leu Gly Gln
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590T
GIN WED FEN TEN GIN LLD FEN WIG LIO BUE CAR WIS WED WIS
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OSOT
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GIY GIY Pro Arg Asp Pro Leu Lys Val Leu Glu Gly Val Val Ala
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                                        TOTO
Ile Met Lys Ile Ile Ser Ala Leu Ser Gly Gly Ser Ala Asp Leu
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Asl Gly Pro Leu Asp Ile Ser Pro Lys Asp Ile Val Gln Ser Ala
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GJM LUL ren ser His ser Phe Ile Leu ser Leu Lys Asn Ser Glu
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Tyr Ala Asp Thr Leu Asn His Leu Glu Lys Ser Leu Ala His Leu
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Yau Ser Glu Asp Glu Ala Glu Glu Ala Lys Asp Ser Lys Val Thr
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006
YIS IIG FAR TAT VAI LYS His PAR IIC Glu LYS PTO ATY LYS ATY
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yla Tyr Asp Val Cys Met Lys Tyr Phe Asp Arg Leu His Pro Gly
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048
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His ren 11e rys Gln Val Pro Gly Ser Ser Pro Glu Trp Leu His
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ren Tyr Thr 11e Trp Leu Gln Lys Leu Phe Trp Thr Gly Asp Pro
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bro Lys Ile Pro Glu Lys Asp Gly Gln Met Leu Ser Pro Ser Ser
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STL
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Cys Ala Asp Leu Gly Asn Cys Ala Ile Lys Pro Glu Thr His Ile
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Hiz Gin yad ren Gin Tyr Tyr Phe Thr Leu Leu Gin Asn Cys Giy
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021.
                    STL
CJu His Wef Ast Tys Tyr Ile Tyr Pro Thr Ile Gly Gly Phe Asp
504
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Asp Ser Gly Leu Ser Thr Leu Glu ile Glu Asn Arg Ala Gln Asp
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MO 01/01/11 LT/Ω200/16948

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Asp Val Leu His Trp Leu Asn Glu Glu Lys Val Ile Gln Arg Leu
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                    SPT
                                         07T
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SET
YJS ZGL byG byG ZGL TAR LJG CJA yzu rGn LJG yJS yLd rAz
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ren lit yeb bie leu kap His Glu Pro Pro Leu Asn Pro Leu Leu
TOR
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GJu IJ6 S6r ysb yrd ren cJA cJA ysb cJn ser ren ren ser ren
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Tys Tyr Pro Asn Thr Ala Cys Glu Leu Leu Thr Cys Asp Val Pro
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Ile Thr Gln Asp Pro Pro Leu Asp Met Glu Glu Lys Val Arg Phe
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YSD bye ren cla yid gju gju cla wer gjn gjn ren naj ser ren
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ysb ysb IJe ren Gju Gjn Cys Lys Ala Gln Asn Gln Lys Leu Leu
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YIS GIN CIY VAI LYS GIN Leu Cys Leu Leu Leu Leu Asn Gin Ser
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ren rys met cys arg ser leu Tyr asn Thr lys Gln met leu Pro
SBTT
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THE ARG CYS THE MEE Glu Asn LYS Glu Gly Leu Gly Asn Glu Val
                    5911
07.TT
Agl Ile Thr Asn Asn Pro Trp Val Arg Leu Ala Thr Val Met Leu
SSTT
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YIY LIO CIN YIY GIN YIY LIO LIO YIY LIO CIN THE THE CIN YIY
099
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yrd cjh cjh cju yeb cjh rhe yjs zer ren cjn yjs Hie yrd yeb
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GIY Ala Pro His Ala Ser Glu Ser Cys Ser Lys Asn Gly Pro Glu
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SEL YED LUL YLG CHE YIS YIS ASI WEL YIS YLG BLO YLG BUG
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ST9
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IJG CJU bio bye yab yab gin yab cin yab Ije Lib cin yab
009
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His Thr Gln Ala Ala Gly Gly Met Arg Arg Gly Asn Met Gly His
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Cys Cys Leu Val Gln Arg ile Leu Glu Ala Trp Glu Ala Asn Asp
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Ala Ser Leu Pro Asp Asn Thr Met Val Thr His Leu Phe Gln Lys
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GFF
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Pro His Glu Asn Gly Asn Arg Ser Leu Glu Thr Pro Gln Pro Ala
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025
GIN GIN YED LYE GIN YIY SEE GIN SEE YED AY GIN LEO
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SOF
                    007
CJU Nal Glu Leu Cys 1le Ala Ala 1le Leu Ser His Ala Ala Arg
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330
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ren yab ren bye bye ria light ligh yan yan bye ren Hia bye
SLE
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261 IJ6 Yzu CJu Cen Cys Arg Leu Asn Thr Met Asp Leu Leu
098
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                                        320
His Gly Ala Arg Leu Met Ala Ala Leu Leu His Thr Asn Thr Pro
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372
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Thr Thr Ile Gly Val Leu Glu Glu Pro Leu Gly Asn Ala Arg Leu
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330
bye His Glu Leu Leu Asn Pro Pro Lys Lys Ala Ile Leu
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Agy Ser Ser Agy Leu His Gly 1le Glu Pro Arg Leu Lys Asp
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OOF
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GJA ren Asi yab ser bhe ser Gin Giy Leu Giu Arg ser Tyr Ala
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GIN Val Leu Leu Thr Leu Clu Thr Arg Ard Val Gly Thr Glu
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WEF BUE YED GIN YED YED LUE GIN ZEE CAE FEN ASI ZEE GIN LUE
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992
YJY TEN GJN SEL YLD GJU YSD CAS AYJ GJN GJU TEN TEN TAS YSU
240
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Cly Ser Gln Leu Gln Glu Ala Leu Glu Pro Asp Pro Leu Leu Thr
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225
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YJ9 ZGL CJu Lyr ren CAz yzb IJ6 A91 Yrd ren GJA yrd yzb CJu
SIO
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Asi cin Leu ile His Pro Ser Gin Asp Giu Asp Arg Gin Ser Asn
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MO 01/01/11 PCL/0/200/19948

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STT
                                        OTT
TSO
YIR GIN THE CHE SEL NET YES TEST FOR YOU GIN THE GIN SEL NET
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Leu Phe Leu Ser Arg Gln Tyr Glu Ser Leu Pro Ala Thr His Ile
06
                    58
Ala Asp Leu Thr Asp Lys Gln Lys His Gln Leu Lys His Arg Glu
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Lys His Ala Lys Glu Ile Glu Glu Glu Ser Glu Thr Thr Val Glu
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                    55
09
Tyr Arg Arg Asp Ile Ser Asn Thr Leu Ile Met Leu Ala Asp
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YEN INE ALE SET GLY ASH VAL GLU ALE LYS VAL VAL CYS PRE
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Val Ser Ser Ala Leu Ala Val Ala Val Pro Leu Gly Pro Ile Met
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882
Thr Thr Ala Leu Ser Lys Ala Gly Pro Ala Ile Pro Thr Pro Ala
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822
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SET ATG LEU LEU SET PTO ALA CYS PTO ALA LIN VAL TAT
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018
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Val Ala Arg Thr Glu Glu Ala Val Gly Arg Val Gly Cys Ala Asp
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852
VIA VAL Ser Arg Gly Pro Gly Arg Glu Ala Pro Pro Pro Thr
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OTS
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Ser His Ser Glu Asp Gly Asp Gln Lys Ala Ala Ser Ala Met Asp
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Yrd rha yly bro ren ren yly ser yab ser ser ser et Gin Gin
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                    SIL
087.
Ala Phe Ser Pro Ala Ser Pro Cys Ala Trp Asn Val Cys Val Thr
59L
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GJN CAZ SEL HIZ YJY GJN GJA SEL YLG SEL GJU GJA LLO GJN TAZ
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                    SŦL
054
Cys Cys Ser Glu Ser Gly Pro Arg Cys Ser Ser Pro Val Asp Thr
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58%
bro GIn Gin Fys Gly Trp Ala Phe Thr Asp Phe Gin Pro Phe
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                                        OTL
Val Arg Asp Val Gly Ser Ser Val Trp Ala Ala Gly Thr Ser Ala
                    00%
                                        569
50L
Asi bhe Asp Glu Pro Ala Asn Ser Thr Pro Thr Ala Pro Gly Val
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                                                             06₽
                                                                                                                             987
96ħ
Gju Asi Cys Lys Asn Thr Leu Arg Leu Arg Gln Ala Arg Arg
                                                                                                                             0 L 7
08₽
                                                             SLF
GJu VJS by6 by6 ren His Thr Thr By6 Thr rys Phe Ala Arg
CQB
                                                             091
                                                                                                                             SST
Pro Val Arg Asn Thr Gly Ser Pro Lys Ser Ala Val Lys Thr Arg
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Pro Arg Val Arg Ser His Val Ser Arg Gln Ala Met Gln Gly Met
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GFB
                                                              0 F T
CJU ZEL GIN GIN CÌN TÀZ PEN ZEL BLO ZEL BLO LUL LUL GIN YZĎ
027
                                                              SIB
                                                                                                                             OID
CAS LID FON LAI LID FAS FAS LAI GJA GJA FON FAS WEF BIO LPI
                                                                                                                             368
                                                             OOF
90£
Tyr Ser Trp Gly Pro Pro Asn Met Gln Cys Arg Leu Cys Ala Ile
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                                                                                                                             380
330
Gly Arg Ala Cys Glu Ser Cys Tyr Ala Thr Gln Ser His Gln Trp
                                                                                                                             392
3.12
                                                             370
Asn Gly Ala Val Gly Thr Thr Phe Gln Pro Gln Asn Pro Leu Leu
                                                              322
                                                                                                                             320
098
yan bro han Gin ile ser Thr ser han Gly bro Gly hia val
                                                                                                                             332
345
                                                             0 Đ £
Gin Ser Lys Leu Lys Gin Val Tyr 1le Pro Thr Tyr Ser Lys Pro
                                                                                                                             320
330
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Thr Asp Arg Tyr Val Gin Gin Lys Arg Leu Lys Ala Ala Giu Ala
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SIE
ras ser leu Tar ser ile ile Glu Tyr Tyr Met Trp Lys Tar
300
                                                                                                                             062
                                                              562
TYT Gly Lys Asp Phe Asn Asp Ile Arg Gln Asp Phe Leu Pro Trp
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285
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Trp Ser Ala Ser Glu Ala Ser Leu Phe Glu Glu Ala Leu Glu Lys
07.7
                                                              592
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552
Leu Tyr Arg His Ser Tyr Asp Leu Ser Ser Ala 11e Ser Val Leu
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0 7 Z
Ala Ala Ser Arg Asp Ile Thr Leu Phe His Ala Met Asp Thr
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Yab Cys Ser Ser Val Arg Gln Pro Ser Leu His Met Ser Ala
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bye ren Asi Asi yis yad yis Asi Ciy Thr Phe Ala Arg Leu
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56T
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Val Trp Asp Pro Asn Ser Pro Leu Thr Asp Arg Gln Ile Asp Gln
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99T
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Yad Asi Gly Pro Ard Tyr Gln Ala Asp Lie Pro Glu Met Leu Leu
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OST
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LAI WED BIO SEI PEN PAR LUI PEN PEN WIS WED PAR GIA GIN IIE
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Pen Ser Tyr Leu Asp Lys Glu Asp Thr Phe Phe Tyr Ser Leu Val
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07Z
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Agy cyn cyn Lyr bro rha rha cha rha yab ije ije rha Lyr yfg
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09
GJn yJs yrd LAr yrd yrd GJn GJA yJs yrd bys IJs bys ysb AsJ
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LEO LÀE 116 GIN WEF YED SEE LEO 116 PEN GIÀ YED LÀE YED YIS
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bye ren ije zer ren ren tyr gið gin kin gin trp val val
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ren Asi yau Gin yau yad bue Cys Asn Asp Ala Met Lys Val Ala
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Ser Ser Arg Leu Pro Glu Phe Ile Val Gln Thr Ala Ser Tyr Met
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bto bto Set CAs bto Asi bto bhe bto Gin Thr Phe Asn Gly Glu
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YIR TEN TEN VAL CYS GIN ATA ALA SET LEN LEU ATA GIN VAL ATA
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07 <007>

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Arg Pro Gln Lys Leu Ile Asn Pro Val Lys Thr Ser Arg Asn His
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SI
Wet Ala Glu Pro Asp Tyr Ile Glu Asp Asp Asn Pro Glu Leu Ile
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Arg Gln Pro Ala Thr His Leu Leu Pro Ser Pro Leu Glu Asp Ser
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Pen bro Thr Gln Ser Pro Leu Ile Leu Leu Gln Gly Trp Ala Cys
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Pro Pro Thr Thr Pro Thr Ser His Pro His Pro His Ala Ser Arg
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Wet Lys Thr Glu Gly Pro Ser Tyr Gly Ala Leu Pro Ala Tyr
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His Gln Leu Gln Gln Pro Pro Ser Leu Gln Pro Thr Pro Gln Val
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Asp Leu Tyr Ser Gln Gly Lys Gln Gln Met Pro His His Thr Pro
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Yab yab yis yab Lyr Asi yab yab LAr GiA yis yab 26r yau 26r
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Gin Gin Asp Gly Met Val Asn His Gly Asp Leu Trp Gly Ser Glu
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TAS TAS GJA LLO GJU ZEL FEN LYE YSU YJY LLO YLA GJA TAS TAS
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rys Leu Pro Lys Gly Ile Ser Ala Gly Ala Val Gln Thr Ala Gly
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yid rha yya yid rha cyu rha cyh yya cyn iyi cyn ren nay yid
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ras ras ser asp Leu Glu Ile Glu Leu Leu Lys Arg Gln Gln Lys
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rks yrg ysb gju ngi ije rks gju rks gjn gjn gja gju rks
09
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<b>→</b> }		

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Ciu Lys Ala Ala Phe Gin Lys Gin Asn Asp Thr Pro Lys Gly Pro
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99/.
yrd yls rha ely val elu Lys eln eln bro elu en pro Phe
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OST
                    STT
IJG CAR PAR AND LAN LAN BY PRO GIU ASP GIU ILE PYO ASP
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                                        152
Yeu Ser Gly Asn Lys Asn Asp Asn Phe Gly Leu Tyr Cys
                    STT
                                        OII
bye ria yau ren cla cys ria beu bro has his has val
                    OOI
                                         96
SOT
Ten Tyr The Arg Asn Phe Arg Cys Asp Cys Gly Asn Ser Lys
Leu Ala Cys Ser Tyr Glu Cys His Gly Ser His Lys Leu Phe Glu
                                         9
CAS SET Thr Cys Thr Pro Glu Gly Glu Glu Pro Ala Gly Ile Cys
                    SS
                                        05
Cys Ser Tyr Ser Gln Gly Ser Val Lys Arg Gln Ala Leu Tyr Ala
                                        32
                    ΩĐ
St
GJn yzu GJn yJy Ckz yJy Nyl ren GJk Gek yzb Zek GJn rkz
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SOT
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rks ije ren bio rks vje cjn his bpe rks wet bio cjn vje cjk
Thr Lys Thr Gly Asp Gly Cys Glu Gly Gly Thr Asp Val Lys Gly
IJE CJU ASI DIO ASP Leu Glu Ala Asp Leu Gln Glu Leu Cys Gln
                   22
                                       05
bto Thr Pro Asp Gln Lys Arg Glu Asp Asp Gln Gly Ala Glu
CĐ
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yab ejn ejn bro rka ejn ejn rka bro bro Thr Lya ser krg kan
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Asi Giy ile Giy Gin Giy Val Pro Val Aai Ala Leu ile Val Giu
56T
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ger Arg Leu Phe Tyr Ser Phe Trp Gly Ser Cys Gln Leu Asp Ser
                   SLT
                                       OLT
ren eju råz ije yzu lyt yta cåz ren bto bye bye zet ren yzb
                   T 0 9 T
                                       SST
GIX YIY GIN NYI FX2 FGN YKA GIU FGN GIN FX2 HIZ IJG ZGK
                   STI
                                       OPT
His Ser His Phe Ile Leu Ala Asp Asn Gly Thr Thr Gly Lys Tyr
                   I30
                                       ISS
Lyr Wet Ser yan Pro Met Ser Lys Leu Thr Val Leu Aan Ser Met
                   STT
                                       TTO
yau cju cjn yab ren 11e cjh yad yab nej nej yad bao Lha cju
SOT
                   OOT
                                       56
GTA TAS ITG CAS THT ITG GIY ITG ALA PTO TTP GLY ILG VAL GLU
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yrd His Nal Gly Asp Ala Leu Lys Asp His Ala Ser Lys Ser Arg
Thr Gly Ala Trp Ile Phe Thr Gly Gly Val Asn Thr Gly Val Ile
                   SS
                                       20
ren ras eju ast bae eja ras eja ren ile ras ala ala met ibr
                   07
                                       35
Ile Ser Val His Gly Gly Leu Gln Asn Phe Glu Leu Gln Pro Lys
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WET TYT VAI ATG VAI SET PRE ASP Thr LYS PTO ASP LEU LEU LEU
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                                        365
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yad bio ser heu Arg heu ber ser Glu Lys ile heu Gly heu Gln
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YED LUK CJU FNE LNK FNE BUG FNE SEK CJU NEJ FNE SEK CJN
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                    340
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yab ren ria in ren bie ren yap His Pro Lys Lys Ile Arg
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330
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CIN WEL LEU LYS GIY Arg Ile Leu Val Gly His Ala Leu His Asn
                                        305
372
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ren riz eju eji ejn ejn ren ejn igi eju riz ejn igi yla
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Asi Thr Asp Tyr Arg Thr Ala Vel Ser Gly ile Arg Pro Glu Asn
582
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                                        SLZ
TYY GLY LYS CYS VAL TYY ASP LYS TYY VAL LYS PYO The Glu Pro
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270
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ras cja cjn cjn ser wet yje yte yte ag ser ije agi ysu cju
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SSZ
Thr Arg Ala Leu Ala Leu Asp Cys Glu Met Val Gly Val Gly Pro
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240
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SEL NY  SEL TEN SEL TEN NY TAS GJN GJU YJY bye GJA GJA TEN
                                        512
225
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ein Ala Ala Lys Ile Ala Arg Lys Gin Leu Gly Gin Ser Giu Gly
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SIO
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bye yab yab Nal Aro Ala Asp Ile Glu Ala Ala Ile Gly Pro
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SGT
Ala Lys Glu Ala Ala Pro Ala Pro Pro Thr Glu Glu Asp Ile Trp
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YED IJG ASI BLO GJN YED GJA HIS FAR FAR FAR FAR
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Cly Thr Clu His Asn Lys Lys Cly Thr Lys Clu Arg Thr Asn Cly
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OST
Ser Lys Met Asp Arg Ala Pro Val Pro Arg Thr Lys Ala Ser
321
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yla Gly Lys Asp Gln Glu Ala Ser Arg Gly Ser Val Pro Ser Gly
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YZU TAR TAR GJN LUL ZGL LLO GJU AYI TAR GJA GJN GJN WGL LLO
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IJG ZGL GJU WGF GJA ZGL FAR FAR FAR FLO FAR IJG IJG GJU GJU
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Lrb ren ren ris eju ris set eju yjg bro ejn ris bro ren vgl
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ras yis pro Glu Asp Phe Ser Gln Asn Trp Lys Ala Leu Gln Glu
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Ser Lys Lys Pro Ala Ser Gly Pro Gly Ala Val Ard Pro Pro
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yau rha rha rha yid bye lip rha ser rha yig yid Gin Nal
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Thr Leu Ser Lys Cys Tyr Leu Pro Arg Glu Asp Val Leu Ile
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yan yan bro ser bhe ile Met Gly ser ile Thr Pro Thr Asp Tyr
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Ytd Asl Pro Glu Leu Ser Val Pro Ser Phe Ser Trp Arg Asn Arg
SIE
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Leu Ser Gly His Thr His Ser Ala Cys Glu Val His His Gly Gly
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Gin Ala Ser Gin Lys Leu Leu Trp Leu Gin Pro Arg Leu Val
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GIN YLD YSD IJG BLO BYG TÀR GIN YSU LÀL YSD NYI TGN 26L YLD
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Ytd Set Ysb Yla Asn Cys Ser Gly Glu Asp Ala Ala Pto Pto Glu
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Gln Yla Glu Leu Ile Glu Val Ser His Arg Leu Asn Cys Ser Arg
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SER ASI YIS TEN YED GIA YED GIA CAS GIA IJE CAS SER GIN LUR
SGI
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GIN Arg Leu Phe Ser Trp Lys Gly ile Asn Phe Val Met Val Asn
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                                         OLT
Wet yan Thr Lys Val Glu Arg Phe Glu Lys Val Phe Ser Ser
59T
                    09T
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ren ras val val Ala Gly Asn His Asp Ile Gly Phe His Tyr Glu
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OST
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Val Glu Arg Phe Gln Lys Met Phe Arg His Pro Ser His Val Gln
SET
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bye yab ejn ejn rna irp ser ihr pro ein hia Trp hia nap asp
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150
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ren 1xb ren ren eju bxo ejn Asj Asj bye ije ren eja yab ije
                    COL
SOT
                                         56
rks ren yzd yxd gjn izb gju wet gjn yzd yjs bye gju iyr yjs
06
                    28
Ala Asp Thr His Leu Leu Gly Glu Phe Leu Gly His Trp Leu Asp
                                         9
                    04
CIY Glu Gln Thr Thr Arg Glu Pro Val Leu Lys Ala Met Phe Leu
                    \varsigma\varsigma
IJe bye GJu C\lambdas ysu L\chib bro GJ\eta NsJ F\lambdas Lyr AJs Ser Ysb
ςĐ
                    0ħ
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bye yla val Leu Leu Pee Cys Glu Phe Leu Ile Tyr Tyr Leu Ala
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ren rks ytd rks zet zet ren ren rks ren ije yjs ngi ng
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Lto His Ser Phe Arg Leu Glu Gly Gly Thr Ala Asp Gly Leu
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yrd ger ije ren ger ras lar ysb gin gin gin gin gin gin yrd
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LAL WIS GIN WED GIN SEL ASI WED FEN WIS GIN FAE DLO
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                                         SOE
Gin Lys Asn Val Giu Leu Arg Lys Lys Lys Pro Asp Tyr Leu Pro
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Cjn yab Nai ren Nai yau Yau ren Nai yab rys Glu Arg Ala
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Gly Leu Thr Val Glu His Ala Ile Asp Ser Phe Arg Glu Gly Glu
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bye cja cju yrd yrd cju yeb ren lar cer yjs yrd yeb ren cju
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GIN WET ASP GIN GIN PAR GIY VAL SET TAT LEU VAL GIU GIU GIU
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Ltb ren yeb yeb Lyr yjs yjs Ltb ije cjn ytd ger yrd cju ren
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yeu cju rke ren cja raz ile rys Thr Leu cly Glu Asp Asp Pro
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egn ren ytd egn riz ren ygg ygg riz en riz ytd ren ren
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OSI
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SET
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GIN GIN IUX YEU TAE TEN YIG YIG TAE TEN GIA TEN TAE LIO TEN
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ISO
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yta ser ser Lys Thr ser ser Gly Asp Ala ser ser Leu ser Ile
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yrd yrd Asj rha yrd Gjn rha yrd yab yab Gjh Lhr Gjn yjs yjs
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SET SET Thr His Gly Arg Glu Arg Ser Gin Pia Gev Gev Glu
51.
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GIY Glu Arg Gly Ser Gly Arg Arg Gly Ala Glu Ala Arg Arg
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GIN GIN SET GIN GIN ATG ATG LYS ATG SET ATG GIN ATG GIN
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YLG His YLG GJN His TWs His TWS His YLG SGK GJW GJW SGK
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450
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Ser Lys Met Leu ile Leu Ser Gin Asn ile Ala Gin Leu Glu Ala
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YSD WEL WEL LYS LYN IDE THE LYS GLU ATG GLU TYF WEL GLY
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Giu Lys Asp Leu Ala Ser Gin Gin Giu Lys Arg Ala Ile Glu Lys
91.8
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CAs wab cju ren wid rat cin ren cin wid cin wid ren
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IJG ZGL CJN CJN YJS YZU bYG CJN TÀZ LYL TÀZ YJS TGN IJG CJU
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CJW YEG CJN YJS SEE YJS LAK CJN CJU ASJ FAR CJU ASJ FEN CJU
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His Wer Gln Thr 11e Glu Arg Leu Val Lys Glu Arg Asp Asp Leu
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Cys Ala Gln His Glu Ala Val Leu Ser Gln Thr His Thr Asn Val
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LYL CYS Glu Asp Leu Lys Glu Gln Leu Lys His Lys Glu Phe Leu
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Ser Gln Leu Lys Phe Leu Arg Asn Asp Leu Ala Glu Tyr Gln Arg
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Gin Lys Leu Lys Teu Thr Giu Giu Lys Cys Giu Ile Giu Giu
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Thr lle Asn Asp Gln Ser Gln Tyr lle His His Leu Glu Ala Glu
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OZT
Glu His Glu Glu Thr Asn Met Pro Thr Met His Asp Leu Val His
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SOT
Val Ser Pro Ser Arg Arg Arg Lys Met Ser Pro Leu Arg Ser Leu
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SL
Ala Arg Thr Ala Trp Pro Glu Leu Gln Gln Ser His Ala Val Asn
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Yap Ala Pro Asn Leu Ser Phe Ser Thr Ser Val Gly Asn Glu Asp
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CJU FEN LUL CAR YIS FEN FAR CJN GIA YED ASJ LUL IJE CJA CJN
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Thr Leu Asn Val His Asp Gly Cys Val Asn Thr 11e Cys Trp Asn
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LAL ren gja yrd yrd gjn bye ije gju yrd ren raz ren gjn yjg
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CJU ren Asi CJU ren ren zer ras CJU yzu CJU ren ren ciu
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SL9
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Thr Tyr Asp Lys Leu Gly Lys Leu Gln Arg Arg Asn Glu Glu Leu
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Tyr Leu Leu Leu Thr Ser Gln Asn Thr Phe Leu Thr Lys Leu Lys
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OTS
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ria Thr Asn Arg Asp Leu Glu Ile Lys Asp Gln Glu Ile Glu Lys
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Wet Gin Lys Asp Glu Ala Glu Lys Glu His Arg Glu Phe Arg Ala
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595
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ren ejn ejn 1je eju zer eju ren vja zer vrg ejn wer vsp val
                    02
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432
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Cln Val Glu Lys Val Thr Lys Glu Lys Ile Ser Ala Ile Asn Gln

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270	e Yu	TIIT.	TPA	ดีรษ	S95	795	785	กรจ	กรอ	260	slA	яζп	TILI.	กรจ
SSS					055					272				
079					555	сŢи	ſsV	zəs	zəg	230	Pro	ſsV	әұа	zəs
GJ <i>n</i>	GŢπ	еŢи	сŢЛ	υĮĐ	26r 230	syj	ςλa	siH	zəs	GJA PJP	əĮI	сŢλ	₽ΊĀ	ser
	zez	slA	IJę	ser		Trp	ejn	<b>ds</b> ¥	дуц	Бу6 200	nsA	ren	sīī	IJę
ДŲД	zez	дуц	дуд	дут	сух	eŢπ	дух	Ser	TYr	siH	$\Gamma$ e $\sigma$	zəs	пәп	Val
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79J	zes	zəs	ько	zes	qsA 091	zəs	сти	siH	siH	Thr Thr	siH	siH	суλ	zes
£ſA 0∂₽	сŢп	Val	zəs	еји	₫₫2 ¥ĸâ	сJп	ејп	Zer	qsA	440 540	zes	zes	пәт	гел
432 5.0	JUJ.	zəs	STH	0.7.4	₹30 26x	กรอ	ı, ı,	ько	zer	425 Ser	дуд	zəs	STH	БIA
<b>₹</b> 50					STD					OTF	ren			
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qsA	стх	¥xā	геп	Arg	ren	Arg	гХз	Val	ько	Pro	стр	yxa	гел	ејп
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**ΜΟ 01/0λ411 LCI/**Ω200/18648

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 {f c}მფმაიამ{f c}მაიამამა აკიამაცია გამაცია გამაციად გამაციამამ ეტე{f c}
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**E6/LL** 

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 ггаддассаг гдадгессаа ддаддеддес аггесаасаа адсеатдгаг дедедадгаг 360
 всягосядго гдвязядгдд госяговдся высможения зобантастр 300
 \mathcal{L}caccccag tatctccgtg cttcagaatg agaaaatga aagtcgcctc tcccgaaatg \mathcal{L}40
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 addeceasas atectagata gaaagageat tttataaaag agaatgtgte cacateatae 120
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  crecces cardedderd radrifter cercracid adedradia acreccide 1440
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  derderard raderecede ededecradr reresdrade esesedeses dedecraeds 1260
  ддваадддас ассссаттся аддадааста тдасдтдстт тсасдддадд сатсасаааа 1200
 restoctety tatoggagaa gigatgetaa cigitetiggg gaagacgetg ctoctecaga 1140
 ರ್ಧ್ಯವೇಡಿತ್ತದೆ ವಿಕ್ಷಂತರಿತದ ಕಡಿದಿಂದಿಂದಿರುತ್ತದೆ ಕಡ್ಡು ಪರ್ಕ್ಷವಿ ಕಡ್ಡಿ ಪರ್ಕ್ಷವಿ ಕ್ಷಣ್ಣ ಪರ್ಧಿ ಪರ್ಕ್ಷವಿ ಕ್ಷಣ್ಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣ್ಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣ್ಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣ್ಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣ್ಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಗಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಗಿ ಕ್ಷಣಣ ಪರ್ಗಿ ಕ್ಷಣಣ ಪರ್ಗಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಗಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರ್ಣ ಪರ್ಣ ಪರ್ಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪರ್ಣ ಪ್ರಕ್ಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರತಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರಕ್ಷವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ರಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ರವಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ರವಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ಷಣಣ ಪ್ರವಿ ಕ್ರವಣ ಪ್ರವಿ ಕ್ರವಣ ಪ್ರವಿ ಕ್ರವಣ ಪ್ರವಿ
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    дсгдааддга дггдсгддаа ассагдасаг тодсгсссаг тагдадагда асасатасаа 840
    адсогавадса авгаягатаа васаагтгся авяяятатгс ваясясссяя агсягатыся 780
    дссадзядес десерсяесс радададные середарая дадзядедая дсясссеры 720
    сваеттасда адудаатудс адатудадад адсутссау асаустстут удтустуса 660
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    \mathsf{r}\mathsf{r}\mathsf{d}\mathsf{d}\mathsf{c}\mathsf{c}\mathsf{c}\mathsf{r}\mathsf{d}\mathsf{s}\mathsf{s} decreased secretate sacctatact \mathsf{2}\mathsf{f}\mathsf{0}
    ctttgctgtg cttctattt gtgaatttt aatctattac ttagcgatct ttcagtgtaa 480
    acagaattt catccattaa agaggaagag ttcattgctg ttgaaactca tagctgttgt 420
    saccettgat ggatttgttg ttgcttgaga aatggcgatg atcgaattgg ggtttggaag 360
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    accaatctct ctgtctttaa aagatgaggt gacttggtga ttttcctgga aaattatagg 240
    адсасддостд геагааагда атгосдагтг гддддадсад атдосаастг ададостодт 180
    aaagggetee egeacegeee ggegeteeee atetgeetgg egttgtgege agagetggaa 120
       მიმიიმმიგი იმმიგმითმი გიიიმმმგიი იგიმმიითიი იმმიიგიი გმიიიგმიმ დე
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гсааттсаду атусссадус аусаатуану стугасуса туугааны уулгы
refergadae ractifeada gaagateett gggeteeagg teeageagge ggageaetgi 1200
aagatteggg acacaegaa atataaacet tteaagagte aagtaaagag tggaaggeeg 1140
стадтудуще асустстуса таатуасста авудтастат тесттуатся тосававая 1080
сөдддөйөөдө адсграваг гагрсыны данасы адагасын адасыны 1050
  вссдвдсссд гдвсддвсгв гвддвсвдсд дгсвдгдддв грсддссгдв дввссрсввд 960
   дсосардар ссерсарде сседрегада ведрасард ведроведре сарсевессе 900
  dccreadccr radactdraa datagtagge gtaggeccta agggggagga gageatggec 840
  3 васдадатья дентинальной соргания 3 васдадатья 3 во 3 
  дагатсдвад стдссатаду гссададусу уссавуны субрания устару 720
  асвавтудьт втаттуться вдаводвиду досатодвид втандавися давадства 600
  ccagtacctc gcaccaaggc cagtggaaca gagcacaata agaaaggaac caaggaaagg 540
  ತತಾರತಂದಾರಿದೆ ತಡಿರಿದಿದಾರಿದ್ದರೆ ಪಡಿರಿದಿದ್ದ ಪ್ರಕ್ಷಣಗಳ ಪ್ರತಿ ಪ್ರಕ್ಷಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ಷಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ಷಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಗಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಗಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ಷಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ಷಣಗಳ ಪ್ರಕ್ಷಣಗಳ ಪ್ರಕ್ರಗಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಣಗಳ ಪ್ರಕ್ರಗಳ 
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  caggococag asaagcotot tgtcatotot cagatgggtt ccaaaaagaa gcccaaaatt 360
  ссядвадаст гегоговав седдавадася седсавадае здоедседва асававает 300
  сдадаядсяя асяядаядсь ядсяядсадь сседардсра радрасдясь ресяявдся 240
  агсявдаедс генеседдня даннанская заданным дагстердня наденаддед 180
  aaggegaagg teceegeete caagegegee eegageagee eegtggetaa geegggteet 120
     ссдддзадасс ддддгсгсдд дгддссдссд дсссяддсдс гддясддсяд сяддягддддд е0
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 дасвадагда вдасвдадсд дсадагдава вадсгадасд вдавдасасг ссгдавдавд 2340
 asactoacac ccaaggagge tttccggcag ctgtcgcace gettccatgg caagggetca 2280
 वन्रपुत्रवित्रवेति वटपुर्वित्तेत्वत वट्टट्विव्यूर्ट वन्नुव्युव्यत्वत वटपुर्विवर्ष्य प्रत्युप्तिव्यत्व प्रत्युप्तिवर्ष
 arddecared ardaeaadra eageeddadd daddaarace dadderreae acaddaerre 2160
 acccadação sadoceces esadecacea ecetesacea egadases 2100
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 даддадсься гддаськьда асдддагдад дадсдсьсад ссаасддьдд сьссдаатсь 1860
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 მშ\zetaშавас\zetaс сессовседсе дроссовсед дроссовед задасдедда дроссовед 1200
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 гтгааааада ссаадсудау уугуаадааа атссусаада аууадааууа уугуу 1320
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 ddccFdcddd sdcdddsdcF ddsddsdsFc cdddccssdcFdcs ddcFcsdfCc TS00
 cdddcedede eesetdtdde dctdcddeed eedecctd ectecctdcc ctatdccded 1020
   999дасардс расуданада даудасард срадранада рауссрадра даурууларданада дау
  дгадаядсяга ссяггдаггс сгрссавдая дадаядасяя гаягрсгряс ссроявдаяс 900
  ರಿತಥಿರಿತರ್ಥಿದು ನಿರ್ದಿತರಿಕೆಂದು ನಿರತಥಿಕ್ಕಾಗಿ ಕಾರತ್ಯಕ್ಕಿಂದ ನಿರ್ದೇಶದ ನಿರ್ದಾಣಕ್ಕೆ 840
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  дасастдсяд ссіддайссда даддадссда садсідсяда аддадавдда ссіддсядад 720
  сгасгдаасс аааадсгада даадагааад ассстаддад аддагдассс сгадсгддас 660
  ತ್ರದ್ದಿರ್ವಿಧ್ಯಕ್ಷಣ ನಿರ್ವಹಿಸಿದ್ದರು ನಿರ್ವಹಿಸಿದ್ದರು ಕ್ರಾಪ್ತಿಸಿದ್ದರು ನಿರ್ವಹಿಸಿದ್ದರು ನಿರ್ವಹಿಸಿದ್ದರು ಕ್ರಾಪ್ತಿಸಿದ್ದರು
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  gargacgget acgaggeege tgecagetee aaaactaget caggegatge etecteaete 420
  сведдасада вдедсвадесь ддевдаесь рессавдедае дедраваед ддядвадедс 3e0
  сагададаса васасадава садасадсас ададосавва сгавадосса двасвод 300
  990csccdd90cddcad 90cddcadc 90cddcaac dacddaadcd dadccdddaa 90c
  გიმმიიმმი\sigma იიმმმმმიმი იყიიმყმიამ იიმიიმიმი ყიიმმმყაიყ იყოფაფაცი ეგე
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# COKRECTED VERSION



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UG, US, UZ, VN, YU, ZA, ZW. RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, IN' 12' 16' KE' KG' KB' KK' KZ' FC' FK' FB' FZ' FL' FN' DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, BY' BB' BG' BK' BK' CY' CH' CN' CK' CN' CS' DE' DK' (81) Designated States (national): AE, AL, AM, AT, AU, AZ,

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(CIP) to earlier applications: (63) Related by continuation (CON) or continuation-in-part

(9991.11.01) 9991 TodmovoN 01 riled on (GID) 743,647 (CIP)  $S\Omega$ 8 September 1999 (08.09.1999) Filed on 60/153,129 (CIP) SN Filed on 12 July 1999 (21.07.1999) 60/145,075 (CIP)

Alto, CA 94304 (US). GENOMICS, INC. [US/US]; 3160 Porter Drive, Palo (71) Applicant (for all designated States except US): INCYTE

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(54) Title: CELL CYCLE AND PROLIFERATION PROTEINS

also provides methods for diagnosing, treating, or preventing disorders associated with expression of CCYPR. and encode CCYPR. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention (57) Abstract: The invention provides human cell cycle and proliferation proteins (CCYPR) and polynucleotides which identify

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### CELL CYCLE AND PROLIFERATION PROTEINS

#### **TECHNICAL FIELD**

This invention relates to nucleic acid and amino acid sequences of cell cycle and proliferation developmental, and cell signaling disorders, and cell proliferative disorders including cancer.

## BACKGROUND OF THE INVENTION

Cell division is the fundamental process by which all living things grow and reproduce. In unicellular organisms such as yeast and bacteria, each cell division doubles the number of organisms, while in multicellular species many rounds of cell division are required to replace cells lost by wear or by programmed cell death, and for cell differentiation to produce a new tissue or organ. Details of the cell division cycle may vary, but the basic process consists of three principal events. The first event, interphase, involves preparations for cell division, replication of the DMA, and production of essential proteins. In the second event, mitosis, the nuclear material is divided and separates to opposite sides of the cell. The final event, cytokinesis, is division and fission of the cell cytoplasm. The sequence and the cell. The final event, cytokinesis, is division and fission of the cell cytoplasm. The sequence and the proteins. In the second event, mitosis, the nuclear material is divided and separates to opposite sides of the cell. The final event, cytokinesis, is division and fission of the cell cytoplasm. The sequence and the proteins are under the control of the cell cytoplasm. The sequence and the protein which controls are under the control of the cell cytoplasms. There are four the protein and of interphase and concludes with the onset of cytokinesis. There are four

Stages in mitosis, occurring in the following order: prophase, metaphase, anaphase and telophase. Prophase includes the formation of bi-polar mitotic spindles, composed of mictrotubules and associated proteins such as dynein, which originate from polar mitotic centers. During metaphase, the nuclear material condenses and develops kinetochore fibers which aid in its physical attachment to the mitotic spindles. The ensuing movement of the nuclear material to opposite poles along the mitotic spindles and develops kinetochore fibers which aid in its physical attachment to the mitotic spindles. The ensuing movement of the nuclear material to opposite poles along the mitotic spindles and bindies. The ensuing anaphase. Telophase includes the disappearance of the mitotic spindles and kinetochore fibers from the nuclear material. Mitosis depends on the interaction of numerous proteins. For segregation 2W10 protein appears to function at the kinetochore as a tension-sensing checkpoint segregation. ZW10 protein appears to function at the kinetochore as a tension-sensing checkpoint segregation. ZW10 protein appears to function at the kinetochore as a tension-sensing checkpoint segregation. ZW10 protein appears to function at the interaction sension set the onset of kinetochore, and, dynein's involvement in the coordination of chromosome separation at the onset of anaphase and/or poleward movement (Start, D.A. et al. (1998) J. Cell Biol. 142:763-774).

Regulated progression of the cell cycle depends on the integration of growth control pathways with the basic cell cycle machinery. Cell cycle regulators have been identified by selecting for human and yeast cDNAs that block or activate cell cycle arrest signals in the yeast mating pheromone pathway

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when they are overexpressed. Known regulators include human CPR (cell cycle progression restoration) genes, such as CPR8 and CPR2, and yeast CDC (cell division control) genes, including tumor suppressor binding proteins, chaperones, transcription factors, translation factors, and RNA-binding proteins (Edwards, M.C. et al. (1997) Genetics 147:1063-1076).

functions in the transition from metaphase to anaphase as well as in the exit from mitosis (Zhao, N. et al. (1998) Genomics 53:184-190). The <u>C. elegans</u> gene cullin-1 (cull) is a negative regulator of the cell cycle. cull regulates the G1 to 5 phase transition and <u>C. elegans</u> cull mutants exhibit hyperplasia of all tissues through acceleration of this transition by overriding mitotic arrest. cull is a member of a conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved gene family that spans <u>S. cerevisiae</u>, nematodes and humans (Kipreos, E.T. et al. (1996) Cell conserved general properties of the conserved general properties of th

Several cell cycle transitions, including the entry and exit of a cell from mitosis, are dependent

The human CDC protein, CDC23, is homologous to the <u>S. cerevisiae</u> protein CDC23 which

upon the activation and inhibition of cyclin-dependent kinases (Cdks). The Cdks are composed of a kinase subunit, Cdk, and an activating subunit, cyclin, in a complex that is subject to many levels of regulation. There appears to be a single Cdk in <u>Saccharomyces cerevisiae</u> and <u>Schizosaccharomyces</u> cyclin-dependent protein kinases which then phosphorylate and activate selected proteins involved in the mitotic process. The Cdk-cyclin complex is both positively and negatively regulated by antiotic process. The Cdk-cyclin complex is both positively and negatively regulated by addition, Cdks are further regulated by binding to inhibitors and other proteins such as Suc1 that addition, Cdks are further regulated by binding to inhibitors and other proteins such as Suc1 that modify their specificity or accessibility to regulators (Patra, D. and W.G. Dunphy (1996) Genes Dev. 10:1503-1515; and Mathias, N. et al. (1996) Mol. Cell Biol. 16:6634-6643).

Reproduction

Meproduction

Meproductive systems are complex and involve many aspects of growth

and development. The anatomy and physiology of the male and female reproductive systems are reviewed in Guyton, A.C. ((1991) <u>Textbook of Medical Physiology</u>, W.B. Saunders Co., Philadelphia PA, pp.899-928).

The male reproductive system includes the process of spermatogenesis, in which the sperm are

formed. Male reproductive functions are regulated by various hormones. The hormones exert their effects on accessory sexual organs, and are involved in cellular metabolism, growth, and other bodily functions.

Spermatogenesis begins at puberty as a result of stimulation by gonadotropic hormones released from the anterior pituitary. Immature sperm (spermatogonia) undergo several mitotic cell

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divisions before undergoing meiosis and full maturation. The testes secrete several male sex hormones. Testosterone, the most abundant, is essential for growth and division of the immature sperm, and for the masculine characteristics of the male body. Three other male sex hormones, gonadotropin-releasing hormone (CnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), control sexual function.

The uterus, ovaries, fallopian tubes, vagina, and breats comprise the female reproductive system. The ovaries and uterus are the source of ova and the location of fetal development, respectively. The fallopian tubes and vagina are accessory organs attached to the top and bottom of the uterus, respectively. Both the uterus and ovaries have additional roles in the development and loss of reproductive capability during a female's lifetime. The primary role of the breasts is lactation. Multiple endocrine signals from the ovaries, uterus, pituitary, hypothalamus, adrenal glands, and other uterus such other and during the female's lifetime. Similarly, the sensitivity of reproductive organs to these endocrine signals varies during the female's lifetime. Similarly, the sensitivity of reproductive organs to these endocrine signals varies during the female's lifetime.

A combination of positive and negative feedback to the ovaries, pituitary and hypothalamus glands controls physiologic changes during the monthly ovulation and endometrial cycles. The anterior pituitary secretes two major gonadotropin hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), regulated by negative feedback of steroids, most notably by ovarian estradiol. If fertilization does not occur, estrogen and progesterone levels decrease. This sudden reduction of the ovarian hormones leads to menstruation, the desquamation of the endometrium.

Hormones further govern all the steps of pregnancy, parturition, lactation, and menopause.

During pregnancy large quantities of human chorionic gonadotropin (hCG), estrogens, progesterone, and human chorionic somatomammotropin (hCS) are formed by the placenta. hCG, a glycoprotein similar to luteinizing hormone, stimulates the corpus luteum to continue producing more progesterone and estrogens, rather than to involute as occurs if the ovum is not fertilized. hCS is similar to growth hormone and is crucial for fetal nutrition.

The female breast also matures during pregnancy. Large amounts of estrogen secreted by the placenta trigger growth and branching of the breast milk ductal system while lactation is initiated by the secretion of prolactin by the pituitary gland.

Parturition involves several hormonal changes that increase uterine contractility toward the end of pregnancy, as follows. The levels of estrogens increase more than those of progesterone. Oxytocin is secreted by the neurohypophysis. Concomitantly, uterine sensitivity to oxytocin increases. The fetus itself secretes oxytocin, cortisol (from adrenal glands), and prostaglandins.

Menopause occurs when most of the ovarian follicles have degenerated. The ovary then

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produces less estradiol, reducing the negative feedback on the pituitary and hypothalamus glands. Mean levels of circulating FSH and LH increase, even as ovulatory cycles continue. Therefore, the ovary is less responsive to gonadotropins, and there is an increase in the time between mensurual cycles. Consequently, mensurual bleeding ceases, and reproductive capability ends.

Tissue growth involves complex and ordered patterns of cell proliferation, cell differentiation,

#### Differentiation and Proliferation

and apoptosis. Cell proliferation must be regulated to maintain both the number of cells and their spatial organization. This regulation depends upon the appropriate expression of proteins which control cell cycle progression in response to extracellular signals, such as growth factors and other mitogens, indirectly modulate cell cycle progression fall into several categories, including growth factors and their indirectly modulate cell cycle progression fall into several categories, including growth factors and their receptors, second messenger and signal transduction proteins, oncogene products, tumor-suppressor proteins, and mitosis-promoting factors.

Embryogenesis is a process in which distinct patterns of protein expression control proper

development. This process involves a host of proteins each with distinct and highly coordinated expression patterns. For example, in the mouse, temporally regulated expression of two related.

Mag1 and Mrg1 contribute to normal embryonic development. Mag1 is expressed in the posterio. domains of the developing mesoderm, while Mrg1 is expressed in the anterior visceral endoderm. Properly coordinated expression of each protein throughout embryogenesis is critical for proper tissue and organ formation (Dunwoodie, S.L. et al. (1998) Mech. Dev. 72:27-40).

Growth factors were originally described as serum factors required to promote cell proliferation. Most growth factors are large, secreted polypeptides that act on cells in their local environment. Growth factors bind to and activate specific cell surface receptors and initiate intracellular signal transduction cascades. Many growth factor receptors are classified as receptor tyrosine kinases which undergo autophosybation upon ligand binding. Autophosyhation enables the receptor to interact with signal transduction proteins characterized by the presence of SH2 or SH3 domains (Src homology regions 2 or 3). These proteins then modulate the activity state of small G-proteins, such as Ras, Rab, and Rho, along with GTPase activating proteins (GAPs), guanine nucleotide releasing proteins (GMRPs), and other guanine modulate the activity state of small Gproteins act as molecular switches that activate other guanine mucleotide exchange factors. Small Gproteins act as molecular switches that activate other downstream events, such as mitogen-activated proteins linease (MAP kinase) cascades. MAP kinases ultimately activate transcription of mitosist pronoting genes.

In addition to growth factors, small signaling peptides and hormones also influence cell proliferation. These molecules bind primarily to another class of receptor, the trimeric G-protein

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stimuli acting on the cell (Smith, A. et al. (1994) Cell 76:959-962; and Nocentini, G. et al. (1997) Proc. SI differentiation and transformation status, which surface receptors are stimulated, and the types of regulate proliferation and differentiation. The celt response depends on the type of cell, its stage of necrosis factor/nerve growth factor (TNF/NGF) family can activate or inhibit cell death, as well as differentiation, migration, or function of cells depending on the circumstance. For example, the tumor besides the regulation of cell growth and division: they can control the proliferation, survival, the same cell at another concentration. Most growth factors also have a multitude of other actions and on other cells to inhibit it. Growth factors may also stimulate a cell at one concentration and inhibit the transforming growth factor beta (TGF-B) family, act on some cells to stimulate cell proliferation often involve activation of kinases and phosphatases. Some growth factors, such as some members of breakdown of other signaling molecules that have direct mitogenic effects. These signaling cascades GPCR-mediated signaling pathways indirectly promote cell proliferation by causing the secretion or levels of intracellular second messengers such as phospholipase C, Ca2+, and cyclic AMP. Most cells. Upon ligand binding, the GPCR activates a trimeric G protein which in turn triggers increased coupled receptor (GPCR), found predominantly on the surface of immune, neuronal and neuroendocrine

inhibition of cell division. Cells often demonstrate an anchorage dependence of cell division as well.

This anchorage dependence may be associated with the formation of focal contacts linking the cytoskeleton with the extracellular matrix (ECM). The expression of ECM components can be stimulated by growth factors. For example, TGF-\$\beta\$ stimulates fibroblasts to produce a variety of ECM proteins, including fibronectin, collagen, and tenascin (Pearson, C.A. et al. (1988) EMBO J. 7:2977-2981). In fact, for some cell types, specific ECM molecules, such as laminin or fibronectin, may act as growth factors. Tenascin-C and -R, expressed in developing and lesioned neural tissue, provide stimulatory/anti-adhesive or inhibitory properties, respectively, for axonal growth (Faisaner, A. (1997) Cell Tissue Res. 290:331-341).

quantities in a perfused system will grow to even higher cell densities before reaching density-dependent

Natl. Acad. Sci. USA 94:6216-6221).

Neighboring cells in a tissue compete for growth factors, and when provided with "unlimited"

Cancers and immune disorders are characterized by uncoordinated cell proliferation. Cancers are associated with the activation of oncogenes which are derived from normal cellular genes. These multant isoforms of the normal protein, and other oncoproteins are abnormally expressed with respect to location or amount of expression. The latter category of oncoproteins are known to affect cell cycle transcriptional control of cell proliferation. Five classes of oncoproteins are known to affect cell cycle controls. These classes include growth factors, growth factor receptors, intracellular signal

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Many oncogenes have been identified and characterized. These include sis, crbA, crbB, hcr-2, proteins involved in cell cycle regulation (Nigg, E.A. (1995) BioEssays 17:471-480). treatment strategy involves reestablishing control over cell cycle progression by manipulation of the changes in the protein complexes that normally control progression through the cell cycle. A primary oncogenes include v-src, v-abl, and v-fps. Certain cell proliferation disorders can be identified by integrated into the human genome after infection of human cells by certain viruses. Examples of viral warsducers, nuclear warscription factors, and cell-cycle control proteins. Viral oncogenes are

cluster region (ber) on chromosome 22. chromosomes 9 and 22 that moves a truncated portion of the proto-oncogene c-abl to the breakpoint and a subset of acute lymphoblastic leukemias, results from a reciprocal translocation between chromosomal translocation. The Philadelphia chromosome, characteristic of chronic myeloid leukemia mdm2, Cip1, p16, and cyclin D. Transformation of normal genes to oncogenes may also occur by mutated G., src, abl, ras, crk, jun, fos, myc, and mutated tumor-suppressor genes such as RB, p53,

Discs-Large, is common to membrane proteins thought to be involved in clustering receptors in growth containing proteins. The PDZ domain, originally described in the Drosophila tumor suppressor protein binding protein, Ras. Recently investigators have shown that Tax interacts with several PDZinclude transformation of primary T-lymphocytes and fibroblasts through cooperation with the a GTPby enhancing the activity of a cellular transcription factor. The oncogenic properties of the Tax protein human T-cell leukemia virus type I (HTLV-1) Tax transactivator protein acts as an early response gene delayed-response genes, which include the cell-cycle regulators Cdk and cyclins. For example, the proteins. These regulatory proteins lead to the transcriptional activation of a second set of genes, the genes. Early-response gene products include myc, fos, and jun, all of which encode gene regulatory growth factors activates two sets of gene products, the early-response genes and the delayed-response Mutations which hyperactivate oncogenes result in cell proliferation. Stimulation of a cell by

Tumor-suppressor genes are involved in regulating cell proliferation. Mutations which cause factor signal transduction pathways (Rousset, R. et al. (1998) Oncogene 16:643-654). 52

Other gene products involved in cell proliferation, differentiation, and apoptosis are yet to be causes it to dissociate from the genes, releasing the suppression, and allowing cell division to proceed. response genes and suppresses their transcription, thus blocking cell division. Phosphorylation of RB example, the retinoblastoma gene product (RB), in a non-phosphorylated state, binds several earlyreduced or loss of function in tumor-suppressor genes result in uncontrolled cell proliferation. For

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screen of human placental cytotrophoblast cells identified 20 genes whose expression levels rose due to comparisons between quiescent and proliferative tissues. For example, a subtractive hybridization discovered. One method currently being utilized to help identify such new molecules involves

EGF induction of cell proliferation. (Morrish, D.W. et al. (1996) Placenta 17:431-441). Another method involves identification of molecules produced in cells treated with anti-tumorigenic agents, such as dithiolethiones. Presumably, the protective action of these anti-tumorigenic agents is associated with the induction of tumor suppressor gene products (Primiano, T. et al. (1996) Carcinogenesis 17:2297-3303).

In another example, the candidate tumor-suppressor gene IMG1, that codes a nuclear protein, p33IMG1, is involved in the negative regulation of cell proliferation. The action of p33IMG1 is dependent upon the activity of another tumor-suppressor gene, p53. p53 is a cellular stress-responsive gene requiring the activity of another tumor-suppressor gene, p53. p53 is a cellular stress-responsive p53 have been shown to physically associate through immunoprecipitation studies (Garkavtsev, I. et al.

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(1998) Nature 391:295-298).

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Apoptosis is the genetically controlled process by which unneeded or defective cells undergo programmed cell death. Selective elimination of cells is as important for morphogenesis and tissue remodeling as is cell proliferation and differentiation. Lack of apoptosis may result in hyperplasia and other disorders associated with increased cell proliferation. Apoptosis is also a critical component of the immune response. Immune cells such as cytotoxic T-cells and natural killer cells prevent the spread of disease by inducing apoptosis in tumor cells and virus-infected cells. In addition, immune cells that at fail to distinguish self molecules from foreign molecules must be eliminated by apoptosis to avoid an autoimmune response.

Apoptotic cells undergo distinct morphological changes. Hallmarks of apoptosis include cell shrinkage, nuclear and cytoplasmic condensation, and alterations in plasma membrane topology. Biochemically, apoptotic cells are characterized by increased intracellular calcium concentration, fragmentation of chromosomal DNA, and expression of novel cell surface components.

The molecular mechanisms of apoptosis are highly conserved, and many of the key protein

regulators and effectors of apoptosis have been identified. Apoptosis generally proceeds in response to a signal which is transduced intracellularly and results in altered patterns of gene expression and protein activity. Signaling molecules such as hormones and cytokines are known both to stimulate and to inhibit apoptosis through interactions with cell surface receptors. Transcription factors also play an important role in the onset of apoptosis. A number of downstream effector molecules, particularly proteases such as the cysteine proteases called caspases, have been implicated in the degradation of cellular components and the proteolytic activation of other apoptotic effectors.

Aging and Senescence Studies of the aging process or senescence have shown a number of characteristic cellular and

molecular changes (Fauci, A.S. et al. (1998) Harrison's Principles of Internal Medicine, McGraw-Hill, New York MY, p.37). These characteristics include increases in chromosome structural abnormalities, DNA cross-linking, incidence of single-stranded breaks in DNA, losses in DNA methylation, and degradation of telomere regions. In addition to these DNA changes, post-translational alterations of proteins increase including deamidation, oxidation, cross-linking, and nonenzymatic glycosylation. Still further molecular changes occur in the mitochondria of aging cells through deterioration of structure.

These changes eventually contribute to decreased function in every organ of the body.

The discovery of new cell cycle and proliferation proteins and the polynucleotides encoding

them satisfies a need in the art by providing new compositions which are useful in the diagnosis,

or prevention, and treatment of immune, developmental, and cell signaling disorders, and cell proliferative

disorders including cancer.

#### SUMMARY OF THE INVENTION

The invention features purified polypeptides, cell cycle and proliferation proteins, referred to

provides an isolated polypeptide comprising the amino acid sequence of SEQ ID MO:1-54. 30 acid sequence selected from the group consisting of SEQ ID NO:1-54. In one alternative, the invention selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the amino acid sequence selected from the group consisting of SEQ ID MO:1-54, b) a naturally occurring 52 isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an "CCYPR-51," "CCYPR-52," "CCYPR-53," "CCYPR-54." In one aspect, the invention provides an 44'», "CCXbK-42'», "CCXbK-46'», "CCXbK-41'», "CCXbK-48'», "CCXbK-48'», "CCXbK-20'» "CCYPR-38," "CCYPR-39," "CCYPR-40," "CCYPR-41," "CCYPR-42," "CCYPR-43," "CCYPR-31," "CCYPR-32," "CCYPR-33," "CCYPR-34," "CCYPR-35," "CCYPR-36," "CCYPR-37," 50 "CCXPR-25," "CCYPR-26," "CCYPR-27," "CCYPR-28," "CCYPR-29," "CCYPR-30," "CTYPR-30," "CCYPR-30," "CCYPR-30," "CCYPR-30," "CCYPR-30," "CCYPR 18'., "CCYPR-19," "CCYPR-20," "CCYPR-21," "CCYPR-22," "CCYPR-23," "CCYPR-24," "CCXPR-12," "CCYPR-13," "CCYPR-14," "CCYPR-15," "CCYPR-16," "CCYPR-17," "CCYPR-"CCYPR-5," "CCYPR-6," "CCYPR-7," "CCYPR-8," "CCYPR-9," "CCYPR-11," "CCYPR-11," collectively as "CCYPR" and individually as "CCYPR-1," "CCYPR-2," "CCYPR-3," "CCYPR-4,"

amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-

The invention further provides an isolated polynucleotide encoding a polypeptide comprising an

54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-54. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:3-54. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:3-5-108.

Additionally, the invention provides a recombinant polynucleotide comprising an amino acid sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% a consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence baving at least 90% a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c) NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c)

20 a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide so expressed.

25 recovering the polypeptide so expressed.

The invention also provides a method for producing a polypeptide comprising an amino acid

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of 3EQ ID NO:1-54, b) a naturally occurring amino acid sequence selected from the group consisting of 3EQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of 3EQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of 3EQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of 3EQ ID NO:1-54.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of

SEQ ID NO:55-108, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence baving at least 70% sequence of identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, c) a naturally occurring polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide or at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide or bragments thereof, and b) detecting the presence or absence of said hybridization complex, and fragments thereof, and b) detecting the presence or absence of said hybridization complex, and popionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

20 target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplification, and b) detecting the presence or said amplified target polynucleotide or fragment thereof, and, optionally, if present, the absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the

The invention further provides a method for detecting a target polynucleotide in a sample, said

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid

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amount thereof.

sequence selected from the group consisting of SEQ ID NO:1-54, and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional CCYPR, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an The invention also provides a method for screening a compound for effectiveness as an

agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The method comprises a) acid sequence selected from the group consisting of SEQ ID NO:1-54. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist activity in the decreased expression of threating and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional CCYPR, comprising administering to a patient in need of such decreased expression of functional CCYPR, comprising administering to a patient in need of such

an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The method of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The method an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The method of an amino acid sequence selected from the group consisting the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical

Additionally, the invention provides a method for screening a compound for effectiveness as

comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional CCYPR, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence selected from the group acid sequence selected from the group

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reatment the pharmaceutical composition.

consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-54. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally occurring amino acid sequence selected from the group consisting of SEQ ID NO:1-54, b) a naturally acid sequence selected from the group consisting of SEQ ID NO:1-54, c) a biologically active fragment of an amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-54, and d) an immunogenic method comprises a) combining the polypeptide with at least one test compound under conditions presence of the test compound under conditions method comprises a) combining the polypeptide in the activity of the polypeptide in the presence of the test compound under conditions of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the absence of the test compound, wherein a compound that modulates the activity of the polypeptide in the absence of the test compound, wherein a compound that modulates the activity of the polypeptide in the absence of the test compound, wherein a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprising a sequence selected from the group consisting of SEQ ID MO:55-108, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said

method comprising a) treating a biological sample containing nucleic acids with the test compound;

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, iii) a naturally occurring polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group sample, said target polynucleotide comprising a polynucleotide sequence selected from the group

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consisting of SEQ ID NO:55-108, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108, iii) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide complementary to ii), and d) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide hybridization complex is amount of hybridization complex in the target polynucleotide biological sample, biological sample, with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

# BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID MOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding CCYPR.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of CCYPR.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression

patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones

encoding CCYPR were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

## DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so

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Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described.

All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

# DELINITIONS

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"CCYPR" refers to the amino acid sequences of substantially purified CCYPR obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of

CCYPR. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of CCYPR either by directly interacting with CCYPR or by acting on components of the biological pathway in which CCYPR participates.

An "allelic variant" is an alternative form of the gene encoding CCYPR. Allelic variants may

result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or an allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides.

Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" mucleic acid sequences encoding CCYPR include those sequences with deletions,

insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as CCYPR or a polypeptide with at least one functional characteristic of CCYPR. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polymorleotide encoding CCYPR, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polymucleotide sequence encoding CCYPR.

30 The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent CCYPR.

Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, and on the basis of similarity in polarity, charge, and on the basis of similarity in polarity, charge, and on the pasis of similarity in polarity, charge, and on the amphipathic nature of the residues, as long as the biological or immunological activity of CCYPR is retained. For example, negatively charged amino biological or immunological activity of CCYPR is retained. For example, negatively charged amino

acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and uncharged side chains and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule,

"Amplification" relates to the production of additional copies of a nucleic acid sequence.

Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of

CCYPR. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of CCYPR either by directly interacting with CCYPR or by acting on components of the biological pathway in which CCYPR participates.

CCYPR participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant.

Antibodies that bind CCYPR polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole impet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as

elicit the immune response) for binding to an antibody.

phosphorothiostes, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the translation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical phospitation of the term "biologically active" refers to a protein having structural, regulatory, or biochemical

functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic CCYPR, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement,

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may composition or an aqueous solution.

Compositions comprising polynucleotide sequences encoding CCYPR or fragments of CCYPR may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated "Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated

DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to

broduce the consensus sequence.

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3'-TCA-5'.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino

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acids which may be substituted for an original amino acid in a protein and which are regarded as

conservative amino acid substitutions.

Val

	1-21	1 4
	īχT	His, Phe, Trp
50	qτT	Phe, Tyr
	щL	ट्ट <b>र</b> , Vबे
	ટ્લ	Суз, Тћг
	ьре	His, Met, Leu, Trp, Tyr
	Met	Len, Ile
· SI	Γλε	Arg, Gln, Glu
	Гeп	ग्रेट, Vब्रो
	эП	Leu, Val
	ziH	Asn, Arg, Gln, Glu
	Gly	slA
10	Glu	Asp, Gln, His
	СJи	Azn, Glu, His
	Cys	Ala, Ser
	qzA	Asn, Glu
	nzA	Asp, Gln, His
ς	g1A	His, Lys
	ßLA	Giy, Ser
-	Original Residue	Conservative Substitution

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide

25 backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation,

(b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the

Ile, Leu, Thr

side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the

absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical

modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

A "fragment" is a unique portion of CCYPR or the polynucleotide encoding CCYPR which is

identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residues. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment

used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the appecification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

specifically identifies SEQ ID NO:55-108, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:55-108 is useful, for SEQ ID NO:55-108 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:55-108 and the region of SEQ ID NO:55-108 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-54 is encoded by a fragment of SEQ ID NO:55-108. A

A fragment of SEQ ID MO:55-108 comprises a region of unique polynucleotide sequence that

fragment of SEQ ID NO:1-54 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-54. For example, a fragment of SEQ ID NO:1-54 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-54.

The precise length of a fragment of SEQ ID NO:1-54 and the region of SEQ ID NO:1-54 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the

intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation codon. (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polynucleotide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polynucleotide sequences.

The terms "percentage of residue matches between at least two polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a

30 standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular

biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191.

For pairwise alignments of polynucleotide sequences, the default parameters are set as follows:

Kluple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several

sources, including the NCBI, Bethesda, MD, and on the Internet at http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST 2 "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below).

"BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST 2 compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

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Gap x drop-off: 50

aligned polynucleotide sequences.

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Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

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Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences in

the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, methods take into account conservative amino acid substitutions. Such conservative substitutions, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to

of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polymucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

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Filter: on

Expect: 10

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, on tragment of at least 15, at least 20, at least 40, at least 50, at least 150 or at least 150 or at least 150 at magnent length size only, and it is understood that any fragment length contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured. "Human artificial chromosomes" (HACs) are linear microchromosomes which may contain "Human artificial chromosomes" (HACs) are linear microchromosomes which may contain

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DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a

complementary strand through base pairing under defined bybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity.

Specific hybridization complexes form under permissive anneating conditions and remain hybridized of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive

SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

 $5^{\circ}$ C to 20°C lower than the thermal melting point ( $T_{\rm m}$ ) for the specific sequence at a defined ionic strength and pH. The  $T_{\rm m}$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_{\rm m}$  and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular

under which the wash step is carried out. Such wash temperatures are typically selected to be about

Generally, stringency of hybridization is expressed, in part, with reference to the temperature

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x 55°C, or 42°C and about 0.1% 5D5, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. 55°C concentration may be varied from about 0.1 to 2 x 55°C, with 5D5 being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as some formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency

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conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., Cot or Rot analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells

or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence

Tesulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular

and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of CCYPR which is

capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of CCYPR which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides,

20 or other chemical compounds on a substrate.
The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other

chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of CCYPR. For example, modulation

may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of CCYPR.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a "Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a

functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

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"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which

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comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of CCYPR.

"Probe" refers to nucleic acid sequences encoding CCYPR, their complements, or fragments

thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oblgonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polynnerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for

example Sambrook, J. et al., 1989, <u>Molecular Cloning: A Laboratory Manual</u>, 2<sup>rd</sup> ed., vol. 1-3, Cold

Spring Harbor Press, Plainview NY; Ausubel, F.M. et al., 1987, <u>Current Protocols in Molecular</u>

Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al., 1990, <u>PCR</u>

Protocols, A <u>Guide to Methods and Applications</u>, Academic Press, San Diego CA. PCR primer pairs

can be derived from a known sequence, for example, by using computer programs intended for that

can be derived from a known sequence, for example, by using computer programs intended for that

Numpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge

MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 5,000 look nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection

those described above. polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to primers, microarray elements, or specific probes to identify fully or partially complementary above selection methods are useful in hybridization technologies, for example, as PCR or sequencing SI polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the Hence, this program is useful for identification of both unique and conserved oligonucleotides and hybridise to either the most conserved or least conserved regions of aligned nucleic acid sequences. UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge 01 their respective sources and modified to meet the user's specific needs.) The PrimeCen program microarrays. (The source code for the latter two primer selection programs may also be obtained from binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer program (available to the public from the Whitchead Institute/MIT Center for Genome Research, and is thus useful for designing primers on a genome-wide scope. The Primer 3 primer selection West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences primer selection program (available to the public from the Genome Center at University of Texas South programs have incorporated additional features for expanded capabilities. For example, the PrimOU

that is made by an artificial combination of two or more otherwise separated segments of sequence.

This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a such recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell. Such a recombinant nucleic acid may be part of a viral vector, e.g., based on a Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence

expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated

vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is

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regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid,

amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding CCYPR, or fragments thereof, or CCYPR itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; genomic DNA, RNA, or

cDMA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or

synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will

reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free,

preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by

different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters,

chips, slides, waters, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polymucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type

30 or tissue under given conditions at a given time.
"Transformation" describes a process by which exogenous DNA is introduced into a recipient

cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type

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of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to

animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or intransgenic organisms contemplated in accordance with the present invention can be cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, t

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at 32 indicative of, for example, a certain population, a disease state, or a propensity for a disease state. which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given polypeptides generally will have significant amino acid identity relative to each other. A polymorphic 30 Species variants are polynucleotide sequences that vary from one species to another. The resulting possess additional functional domains or lack domains that are present in the reference molecule. due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant 57 sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the 20

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least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

## THE INVENTION

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The invention is based on the discovery of new human cell cycle and proliferation proteins (CCYPR), the polynucleotides encoding CCYPR, and the use of these compositions for the diagnosis, treatment, or prevention of immune, developmental, and cell signaling disorders, and cell proliferative disorders including cancer.

Table I lists the Incyte clones used to assemble full length nucleotide sequences encoding CCYPR. Columns I and 2 show the sequence identification numbers (SEQ ID MOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each CCYPR were identified, and column 4 shows the cDNA libraries from uncleic acids encoding each CCYPR were identified, and column 4 shows the cDNA libraries from libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. CenBank sequences, where indicated, in column 5 were used to assemble the consensus nucleotide sequence of each CCYPR and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention:

column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis along with relevant citations, all of which are expressly incorporated by reference herein in their entirety; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods and in some cases, searchable databases to which the analytical methods were applied. The protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding CCYPR. The first column of Table 3 lists the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:55-108 and to distinguish between SEQ ID NO:55-108 and related polynucleotide sequences. The polypeptides to distinguish between SEQ ID NO:55-108 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue

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categories which express CCYPR as a fraction of total tissues expressing CCYPR. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing CCYPR as a fraction of total tissues expressing CCYPR. Column 5 lists the vectors used to subclone each cDNA library. Of particular note is the expression of SEQ ID NO:66 in inflammatory tissues. It should be noted that SEQ ID NO:76 was found to be expressed predominantly in nervous tissue.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding CCYPR were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:61 maps to chromosome 5 within the interval from 141.40 to 142.60

centiMorgans. This interval also contains gene(s) and/or EST(s) associated with corneal dystrophy and deafness.

SEQ ID NO:73 maps to chromosome 2 within the interval from 73.80 to 83.50 centiMorgans. This interval also contains gene(s) and/or EST(s) associated with hereditary nonpolyposis colorectal carcinoma and Muir-Torre syndrome. SEQ ID NO:74 maps to chromosome 19 within the interval from 41.70 to 58.70 centiMorgans. This interval also contains gene(s) and/or EST(s) located within the human breast cancer (BRCA1) gene region. SEQ ID NO:76 maps to chromosome 1 within the interval from 143.30 to 153.90 centiMorgans, to chromosome 3 within the interval from 156.20 to 160.00 centiMorgans, and to chromosome X within the interval from 112.80 to 139.40 centiMorgans. The interval on chromosome X from 112.80 to 139.40 centiMorgans.

centiMorgans, and to chromosome 11 within the interval from 136.90 centiMorgans to q-terminus.

EST(s) associated with X-linked agammaglobulinaemia.

SEQ ID NO:77 maps to chromosome 23 within the interval from 173.60 to 179.80

SEQ ID NO:78 maps to chromosome 3 within the interval from 167.60 centiMorgans to q-terminus.

SEQ ID NO:81 maps to chromosome 7 within the interval from 167.60 centiMorgans to q-terminus.

SEQ ID NO:90 maps to chromosome 2 within the interval from 236.10 to 240.20 centiMorgans, to chromosome 3 within the interval from 16.50 to 43.00 centiMorgans, SEQ ID NO:91 maps to chromosome 6 within the interval from 124.20 to 126.50 centiMorgans. SEQ ID NO:98 maps to chromosome 2 within the interval from 40.30 to 60.00 centiMorgans. SEQ ID NO:100 maps to chromosome 8 within the interval from 40.30 to 60.00 centiMorgans. SEQ ID NO:100 maps to chromosome 14 within the interval from 32.40 centiMorgans to q-terminus. SEQ ID NO:104 maps to chromosome 18 within the interval from 32.40 to 42.70 centiMorgans. SEQ ID NO:105 maps to chromosome 18 within the interval from 32.40 to 42.70 centiMorgans. SEQ ID NO:105 maps to chromosome 19 within the interval from 32.40 to 42.70 centiMorgans.

81.20 centiMorgans.

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The invention also encompasses CCYPR variants. A preferred CCYPR variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the CCYPR amino acid sequence, and which contains at least one functional or structural characteristic of CCYPR.

The invention also encompasses polynucleotides which encode CCYPR. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:55-108, which encodes CCYPR. The polynucleotide sequences of SEQ ID NO:55-108, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding CCYPR. In

particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding CCYPR. A particular aspect of the invention encompasses a variant of a polynucleotide sequence selected from the group consisting of SEQ ID NO:55-108 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:55-108. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of CCYPR.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding CCYPR, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring CCYPR, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode CCYPR and its variants are generally capable of

hybridizing to the nucleotide sequence of the naturally occurring CCYPR under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding CCYPR or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide

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sequence encoding CCYPR and its derivatives without altering the encoded amino acid sequences

include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode CCYPR and

CCYPR derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding CCYPR or any fragment thereof.

hybridizing to the claimed polymucleotide sequences, and, in particular, to those shown in SEQ ID NO:55-108 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Also encompassed by the invention are polynucleotide sequences that are capable of

Methods for DNA sequencing are well known in the art and may be used to practice any of the

Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.) Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in 52 CA), or other systems known in the art. The resulting sequences are analyzed using a variety of (PE Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (PE automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), 50 amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway VI), or DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of ςį

The nucleic acid sequences encoding CCYPR may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.)
Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a sequence from a circularized template.

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kes. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequences sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, 1.D. et al. (1991) Nucleic Acids Res. 19:3055-3060).

Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Additionally) on another appropriate program, to be about 22 to 30 nucleotides in length, to have a CC content of about 50% or more, and to another to the template at temperatures of about 68°C to

When screening for full-length cDMAs, it is preferable to use libraries that have been size-selected to include larger cDMAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDMA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the

size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotides specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

encode CCYPR may be cloned in recombinant DNA molecules that direct expression of CCYPR, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express CCYPR.

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The nucleotide sequences of the present invention can be engineered using methods generally

In another embodiment of the invention, polynucleotide sequences or fragments thereof which

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known in the srt in order to alter CCYPR-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotidemants of the present introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such alter and the present invention may be subjected to DNA shuffling techniques such as the present invention may be subjected to DNA shuffling techniques such as the present invention may be subjected to DNA shuffling techniques such as the present invention may be subjected to DNA shuffling techniques such as the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling techniques and the present invention may be subjected to DNA shuffling the present invention may be subjected to DNA shuffling the present invention may be subjected to DNA shuffling the present invention may be subjected to DNA shuffling the present invention may be subjected to DNA shuffling the present the pr

as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of CCYPR, such as its biological or enzymatic activity or its ability variants is produced using PCR-mediated recombination of gene fragments. The library of gene subjected to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and contollable maximished on the same genetic diversity of multiple naturally occurring genes in a directed and contollable

CCYPR itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) <u>Proteins, Structures and Molecular Properties</u>, WH Freeman, New York NY, pp. 55-60; and Roberge, 1.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequences of using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequences of using part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

using chemical methods well known in the art. (See, e.g., Caruthæs, M.H. et al. (1980) Mucleic Acids Symp. Ser. 7:225-232.) Alternatively, Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Mucleic Acids Symp. Ser. 7:225-232.)

manner.

In another embodiment, sequences encoding CCYPR may be synthesized, in whole or in part,

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.)

The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, <u>supra</u>, pp. 28-53.)

In order to express a biologically active CCYPR, the nucleotide sequences encoding CCYPR or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding CCYPR. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding CCYPR. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where

sequences encoding CCYPR and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding CCYPR and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995)

Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences

encoding CCYPR. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., Ti or pBR322 plasmids); or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, <u>supra</u>; Ausubel, <u>supra</u>; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; Scorer, C.A. et al. (1994) BiolTechnology 12:181-184; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu,

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N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di dicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al., (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.)

The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding CCYPR. For example, routine cloning, substantial propagation of polynucleotide sequences encoding CCYPR can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORTI plasmid disrupts the lacZ gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vinco deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) I. Biol. Chem. 264:5503-5509.) When large quantities of CCYPR increase, G. and S.M. Schuster (1989) I. Biol. Chem. vectors which direct high level expression of CCYPR increased. E.g. for the production of antibodies, the strong, inducible T5 or T7 bacteriophage promoter may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast <u>Saccharomyces cerevisiae</u> or <u>Pichia pastoria</u>. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, <u>supra</u>; Bitter, <u>supra</u>; and Scorer, <u>supra</u>.)

Yeast expression systems may be used for production of CCYPR. A number of vectors

Plant systems may also be used for expression of CCYPR. Transcription of sequences

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encoding CCYPR may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated

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Transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases

where an adenovirus is used as an expression vector, sequences encoding CCYPR may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses CCYPR in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of

CCYPR in cell lines is preferred. For example, sequences encoding CCYPR can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in tk and apr cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, dhfr confers resistance to methorrexate; neo confers resistance to the aminoglycosides neomycin and G-418; and als and pat confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., trpB and hisD, which alter cellular requirements

Any number of selection systems may be used to recover transformed cell lines. These include,

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for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), B

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(1995) Methods Mol. Biol. 55:121-131.) transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. These markers can be used not only to identify transformants, but also to quantify the amount of glucuronidase and its substrate b-glucuronide, or luciferase and its substrate luciferin may be used.

promoter. Expression of the marker gene in response to induction or selection usually indicates marker gene can be placed in tandem with a sequence encoding CCYPR under the control of a single sequences encoding CCYPR can be identified by the absence of marker gene function. Alternatively, a sequence encoding CCYPR is inserted within a marker gene sequence, transformed cells containing also present, the presence and expression of the gene may need to be confirmed. For example, if the Although the presence/absence of marker gene expression suggests that the gene of interest is

CCYPR may be identified by a variety of procedures known to those of skill in the art. These In general, host cells that contain the nucleic acid sequence encoding CCYPR and that express

expression of the tandem gene as well.

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Immunological methods for detecting and measuring the expression of CCYPR using either chip based technologies for the detection and/or quantification of nucleic acid or protein sequences. amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR

specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include

York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.) 52 et al. (1997) <u>Current Protocols in Immunology</u>, Greene Pub. Associates and Wiley-Interscience, New al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MM, Sect. IV; Coligan, J.E. assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et antibodies reactive to two non-interfering epitopes on CCYPR is preferred, but a competitive binding activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal 50 enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence

commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase for the production of an mRNA probe. Such vectors are known in the art, are commercially available, Alternatively, the sequences encoding CCYPR, or any fragments thereof, may be cloned into a vector oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. or PCR probes for detecting sequences related to polynucleotides encoding CCYPR include may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization A wide variety of labels and conjugation techniques are known by those skilled in the art and

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(Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding CCYPR may be cultured under

conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode CCYPR may be designed to contain signal sequences which direct secretion of CCYPR through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities which have specific cellular machinery and characteristic mechanisms for post-translational activities which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and W138) are available from the American Type Culture of the foreign protein.

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In another embodiment of the invention, natural, modified, or recombinant nucleic acid

expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially may be cleaved away from the heterologous moiety following purification. Methods for fusion protein located between the CCYPR encoding sequence and the heterologous protein sequence, so that CCYPR these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize 30 respectively. FLAG, c-myc, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, c-myc, and matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose 52 peptide moieties may also facilitate purification of fusion proteins using commercially available affinity facilitate the screening of peptide libraries for inhibitors of CCYPR activity. Heterologous protein and containing a heterologous moiety that can be recognized by a commercially available antibody may fusion protein in any of the aforementioned host systems. For example, a chimeric CCYPR protein sequences encoding CCYPR may be ligated to a heterologous sequence resulting in translation of a 70

available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled CCYPR may be achieved in

vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for

example,  $^{35}$ S-methionine. CCYPR of the present invention or fragments thereof may be used to screen for compounds that specifically bind to CCYPR. At least one and up to a plurality of test compounds may be

In one embodiment, the compound thus identified is closely related to the natural ligand of

screened for specific binding to CCYPR. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

CCYPR, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, Coligan, I.E. et al. (1991) Current Protocols in Immunology 1(2):

Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which CCYPR compounds or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the these compounds involves producing appropriate cells which express CCYPR, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. Coli. Cells expressing CCYPR or cell membrane fractions which contain CCYPR are then contacted with a test compound and binding, simulation, or inhibition of activity of either CCYPR or the with a test compound and binding, simulation, or inhibition of activity of either CCYPR or the

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with CCYPR, either in solution or affixed to a solid support, and detecting the binding of a test compound in the presence of a Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a

OCYPR of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of CCYPR. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for CCYPR activity, wherein CCYPR is compined with at least one test compound, and the activity of CCYPR in the presence of a test compound is compared with the activity of CCYPR in the absence of the test compound. A change in the activity of CCYPR in the presence of the test compound is

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compound is analyzed.

indicative of a compound that modulates the activity of CCYPR. Alternatively, a test compound is combined with an <u>in vitro</u> or cell-free system comprising CCYPR under conditions suitable for CCYPR activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of CCYPR may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding CCYPR or their mammalian homologs

heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential 70 to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific SI genome by homologous recombination. Alternatively, homologous recombination takes place using (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. embryo and grown in culture. The ES cells are transformed with a vector containing the gene of example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal may be "knocked out" in an animal model system using homologous recombination in embryonic

Polynucleotides encoding CCYPR may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate

(1998) Science 282:1145-1147). Polynucleotides encoding CCYPR can also be used to create "knockin" humanized animals

(pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding CCYPR is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transgenic progeny or inbred lines are studied and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress CCYPR, e.g., by secreting CCYPR in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-

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therapeutic or toxic agents.

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Therefore, in one embodiment, CCYPR or a fragment or derivative thereof may be 10 increase the expression or activity of CCYPR. treatment of disorders associated with decreased CCYPR expression or activity, it is desirable to CCYPR expression or activity, it is desirable to decrease the expression or activity of CCYPR. In the proliferative disorders including cancer. In the treatment of disorders associated with increased CCYPR appears to play a role in immune, developmental, and cell signaling disorders, and cell CCYPR is closely associated with inflammation, trauma, cell proliferation and cancer. Therefore, between regions of CCYPR and cell cycle and proliferation proteins. In addition, the expression of Chemical and structural similarity, e.g., in the context of sequences and motifs, exists

activity of CCYPR. Examples of such disorders include, but are not limited to, an immune disorder

administered to a subject to treat or prevent a disorder associated with decreased expression or

sensorineural hearing loss, and disorders of immune cell activation; a cell signaling disorder including and cerebral palsy, spina bifida, anencephaly, craniorachisis, congenital glaucoma, cataract, neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and: mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, lymphoma, leukemia, and myeloma; a developmental disorder such as renal tubular acidosis, anemia, tungal, parasitic, protozoal, and helminthic infections, trauma, and hematopoietic cancer including syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, imitable bowel syndrome, mixed connective tissue disorder (MCTD), multiple sclerosis, myasthenia disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, 70 егупьета поdosum, аторhic gastriús, glomerulonephriús, Goodpasture's syndrome, gout, Graves' diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, bursitis, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, SI disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's

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thymus, thyroid, and uterus. lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, 52 ргітату гілготоосульстів, ала сапсет ілсічаіпу адепосатсіпота, ісикетів, іутрілота, теїалота, disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue impotence, carcinoma of the male breast, and gynecomastia; and a cell proliferative disorder such as cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, 20 receptors, syndrome of 5  $\alpha$ -reductase, a disruption of spermatogenesis, abnormal sperm physiology, associated with Leydig cell tumors, androgen resistance associated with absence of androgen men, Leydig cell deficiency, male climacteric phase, germinal cell aplasia, hypergonadal disorders breast cancer, and fibrocystic breast disease; and, in post-menopausal women, osteoporosis; and, in gonadotropin deficiency, amenorrhea, galactorrhea, hermaphroditism, hirzutism and virilization, SI fibroid, autoimmune disorders, an ectopic pregnancy, teratogenesis, hyperprolactinemia, isolated ovarian disease, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine tubal disease, ovulatory defects, and endometriosis, perturbations of the menstrual cycle, polycystic gonadal steroid hormones such as: in women, abnormal prolactin production, infertility, including adenoma of the adrenal cortex, hypertension associated with alkalosis; disorders associated with 01 associated complications; disorders associated with the adrenals such as hyperplasia, carcinoma, or disease (chronic hypercalemia); pancreatic disorders such as Type II diabetes mellitus and associated with bacterial infection; disorders associated with hyperparathyroidism including Conn adenoma; disorders associated with hypothyroidism including goiter, myxedema, acute thyroiditis syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) often caused by benign head trauma; disorders associated with hyperpituitarism including acromegaly, giantism, and vascular malformations, thrombosis, infections, immunological disorders, and complications due to primary brain tumors, adenomas, infarction associated with pregnancy, hypophysectomy, aneurysms, endocrine disorders such as disorders of the hypothalamus and pituitary resulting from lesions such as

In another embodiment, a vector capable of expressing CCYPR or a fragment or derivative

In a further embodiment, a pharmaceutical composition comprising a substantially purified expression or activity of CCYPR including, but not limited to, those described above. thereof may be administered to a subject to treat or prevent a disorder associated with decreased

limited to, those provided above. or prevent a disorder associated with decreased expression or activity of CCYPR including, but not CCYPR in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat

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In still another embodiment, an agonist which modulates the activity of CCYPR may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of CCYPR including, but not limited to, those listed above.

In a further embodiment, an antagonist of CCYPR may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of CCYPR. Examples of such disorders include, but are not limited to, those immune, developmental, and cell signaling disorders, and cell proliferative disorders including cancer, described above. In one aspect, an antibody which specifically binds CCYPR may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express CCYPR.

In an additional embodiment, a vector expressing the complement of the polynucleotide approach a complement of the polynucleotide.

encoding CCYPR may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of CCYPR including, but not limited to, those described above. In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary

sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various of therapeutic efficacy with disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of CCYPR may be produced using methods which are generally known in the

art. In particular, purified CCYPR may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind CCYPR. Antibodies to CCYPR may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies. Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

and others may be immunized by injection with CCYPR or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans,

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CCYPR have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of CCYPR amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be fused with those of another protein, such as KLH, and antibodies to the

Monoclonal antibodies to CCYPR may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J.

Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. 13 Matl. Acad. Sci. USA 81:6851-6855; Meuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, Chain antibodies may be adapted, using methods known in the art, to produce CCYPR-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing <u>in vivo</u> production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for CCYPR may also be generated.

For example, such fragments include, but are not limited to, F(ab')<sub>2</sub> fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')<sup>2</sup> fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. 30 (1989) Science 246:1275-1281.)

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Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoassays typically involve the measurement of complex formation between CCYPR and its immunoassays typically involve the measurement of complex formation between CCYPR and its

specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering CCYPR epitopes is generally used, but a competitive binding assay may also be employed (Pound, <u>supra</u>).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine Cryct (1991) <u>A Practical Guide to Monoclonal Antibodies</u>, John Wiley & Sons, New York NY). (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. ultimately require dissociation of CCYPR, preferably in active form, from the antibody (Catty, D. about 10° to 10' L/mole are preferred for use in immunopurification and similar procedures which must withstand rigorous manipulations. Low-affinity antibody preparations with K, ranging from about 10° to 1012 L/mole are preferred for use in immunoassays in which the CCYPR-antibody complex epitope, represents a true measure of affinity. High-affinity antibody preparations with K, ranging from determined for a preparation of monoclonal antibodies, which are monospecific for a particular CCYPR 01. CCYPR epitopes, represents the average affinity, or avidity, of the antibodies for CCYPR. The  $K_{\bullet}$ for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple molar concentrations of tree antigen and tree antibody under equilibrium conditions. The K, determined constant, K<sub>n</sub>, which is defined as the molar concentration of CCYPR-antibody complex divided by the may be used to assess the affinity of antibodies for CCYPR. Affinity is expressed as an association ς

the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, is generally employed in procedures requiring precipitation of CCYPR-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, <u>supra</u>, and Coligan et al., <u>supra</u>.)

In another embodiment of the invention, the polynucleotides encoding CCYPR, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding CCYPR. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding CCYPR. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense

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sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence

complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) J. Allergy Clin. Immunol. 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-XI disease characterized by X-linked

In another embodiment of the invention, polynucleotides encoding CCYPR may be used for

inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), Crystal, R.G. et al. (1995) Science 270:470-475), Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and Somia, N. (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatilis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides of the analysis of the conditional parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in CCYPR expression or regulation causes disease, the expression of CCYPR from an appropriate population of transduced cells may alleviate the clinical manifestations.

OCYPR are treated by constructing mammalian expression vectors encoding CCYPR and introducing these vectors by mechanical means into CCYPR-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-10; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol.

caused by the genetic deficiency.

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In a further embodiment of the invention, diseases or disorders caused by deficiencies in

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Expression vectors that may be effective for the expression of CCYPR include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Suzasgene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). CCYPR may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β-actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the PK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and H.M. Blau, 1998), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding CCYPR from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (Graham) Ebber 1:841-845). The introduction of DNA to primary cells requires modification of these

standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to CCYPR expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding CCYPR under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RMA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus cis-acting RMA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBMEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Mail. Acad. Sci. USA 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 72:8463-8471; Zufferey, R. A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining"

retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference.

Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4\* T-cells), and the teturn of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. USA 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver.

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver.

polynucleotides encoding CCYPR to cells which have one or more genetic abnormalities with respect to the expression of CCYPR. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annumeteby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annumeteby incorporated by reference herein.

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In another alternative, a herpes-based, gene therapy delivery system is used to deliver

containing different segments of the large herpesvirus genomes, the growth and propagation of sequences, the generation of recombinant virus following the transfection of multiple plasmids Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. the control of the appropriate promoter for purposes including human gene therapy. Also taught by this d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is Res. 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. 52 been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has ropism. The construction and packaging of herpes-based vectors are well known to those with especially valuable for introducing CCYPR to cells of the central nervous system, for which HSV has a respect to the expression of CCYPR. The use of herpes simplex virus (HSV)-based vectors may be 70 polynucleotides encoding CCYPR to target cells which have one or more genetic abnormalities with

skill in the art.

infections, are well known to those with ordinary skill in the art. of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus require the sorting of cells prior to transduction. The methods of manipulating infectious cDMA clones CCYPR into a variety of cell types. The specific transduction of a subset of cells in a population may et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic typically associated with cell lysis within a few days, the ability to establish a persistent infection in and the synthesis of high levels of CCYPR in vector transduced cells. While alphavirus infection is place of the capsid-coding region results in the production of a large number of CCYPR-coding RMAs and polymerase). Similarly, inserting the coding sequence for CCYPR into the alphavirus genome in overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the RAA replication, a subgenomic RAA is generated that normally encodes the viral capsid proteins. This the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotech. 9:464-469). During alphavirus Semilid Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on deliver polynuclectides encoding CCYPR to target cells. The biology of the prototypic alphavirus, In another alternative, an alphavirus (positive, single-stranded RWA virus) vector is used to

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, complementary sequence or antisense molecules may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RMA molecules, may also be used to catalyze the specific cleavage of RMA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RMA, followed by endonucleolytic cleavage. For example, endonucleolytic cleavage of sequences encoding CCYPR.

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Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis.

Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding CCYPR. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Atternatively, these cDNA constructs that suitable RNA polymerase promoters such as T7 or SP6. Atternatively, these cDNA constructs that suitable RNA polymerase promoters such as T7 or SP6. Atternatively, these cDNA constructs that

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by

RMA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PMAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a

Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased CCYPR expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding CCYPR may be therapeutically useful, and in the treament of disorders associated with decreased CCYPR expression or activity, a compound which specifically promotes associated with decreased CCYPR expression or activity, a compound which specifically promotes expression of the polynucleotide encoding CCYPR may be therapeutically useful.

compound which is effective in altering expression of a polynucleotide encoding CCYPR.

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At least one, and up to a plurality, of test compounds may be screened for effectiveness in

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Many methods for introducing vectors into cells or tissues are available and equally suitable for 52 Patent No. 6,022,691). sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a 50 Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Amdt, G.M. et al. (2000) Nucleic Acids polynucleotide can be carried out, for example, using a <u>Schizosaccharomyces pombe</u> gene expression the polynucleotide. A screen for a compound effective in altering expression of a specific exposed to a test compound indicates that the test compound is effective in altering the expression of exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide forming the basis for a comparison of the expression of the polynucleotide both with and without of the polynucleotide encoding CCYPR. The amount of hybridization may be quantified, thus detected by hybridization with a probe having a nucleotide sequence complementary to the sequence by any method commonly known in the art. Typically, the expression of a specific nucleotide is 10 biochemical system. Alterations in the expression of a polynucleotide encoding CCYPR are assayed may comprise, for example, an intact or permeabilized cell, or an in vitto cell-free or reconstituted polynucleotide encoding CCYPR is exposed to at least one test compound thus obtained. The sample library of chemical compounds created combinatorially or randomly. A sample comprising a based on chemical and/or structural properties of the target polynucleotide; and selection from a ς library of naturally-occurring or non-natural chemical compounds; rational design of a compound altering polynucleouide expression; selection from an existing, commercially-available or proprietary commonly known in the art, including chemical modification of a compound known to be effective in altering expression of a specific polynucleotide. A test compound may be obtained by any method

Many methods for introducing vectors into cells or tissues are available and equally suitable four use in vivo, in vivo, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutically composition which generally comprises an active ingredient formulated with a pharmaceutically

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acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Goiences (Maack Publishing, Easton PA). Such pharmaceutical compositions may consist of CCYPR, antibodies to CCYPR, and mimetics, agonists, or inhibitors of CCYPR.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intraventicular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranscal, enteral, topical, sublingual, or rectal means.

Pharmaceutical compositions for pulmonary administration may be prepared in liquid or dry

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powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., and the lungerion, 1.5. et al., U.5. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the

active ingredients are contained in an effective amount to achieve the intended purpose. The

Specialized forms of pharmaceutical compositions may be prepared for direct intracellular

delivery of macromolecules comprising CCYPR or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, CCYPR or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for

administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example CCYPR or fragments thereof, antibodies of CCYPR, and agonists, antagonists or inhibitors of CCYPR, which

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The exact dosage will be determined by the practitioner, in light of factors related to the subject sensitivity of the patient, and the route of administration. 10 or no toxicity. The dosage varies within this tange depending upon the dosage form employed, the compositions is preferably within a range of circulating concentrations that includes the  ${
m ED}_{50}$  with little studies are used to formulate a range of dosage for human use. The dosage contained in such exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal therapeutic index, which can be expressed as the LD<sub>50</sub>/ED<sub>50</sub> ratio. Pharmaceutical compositions which lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the calculating the  $\mathrm{ED}_{50}$  (the dose therapeutically effective in 50% of the population) or  $\mathrm{LD}_{50}$  (the dose standard pharmaceutical procedures in cell cultures or with experimental animals, such as by ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by

Normal dosage amounts may vary from about 0.1  $\mu g$  to 100,000  $\mu g$ , up to a total dose of biweekly depending on the half-life and clearance rate of the particular formulation. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. of the disease state, the general health of the subject, the age, weight, and gender of the subject, time moiety or to maintain the desired effect. Factors which may be taken into account include the severity requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active

inhibitors. Similarly, delivery of polynucleoudes or polypeptides will be specific to particular cells, Those skilled in the art will employ different formulations for nucleotides than for proteins or their methods of delivery is provided in the literature and generally available to practitioners in the art. about I gram, depending upon the route of administration. Guidance as to particular dosages and

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conditions, locations, etc.

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pe nzeq wide variety of reporter molecules, several of which are described above, are known in the art and may modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without 30 Diagnostic assays for CCYPR include methods which utilize the antibody and a label to detect CCYPR. diagnostic purposes may be prepared in the same manner as described above for therapeutics. treated with CCYPR or agonists, antagonists, or inhibitors of CCYPR. Antibodies useful for diagnosis of disorders characterized by expression of CCYPR, or in assays to monitor patients being In another embodiment, antibodies which specifically bind CCYPR may be used for the

A variety of protocols for measuring CCYPR, including ELISAs, RIAS, and FACS, are known

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in the art and provide a basis for diagnosing altered or abnormal levels of CCYPR expression. Normal or standard values for CCYPR expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to CCYPR under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of CCYPR expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values.

Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polymucleotides encoding CCYPR may be used for

diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of CCYPR, and to monitor regulation of CCYPR levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide

sequences, including genomic sequences, encoding CCYPR or closely related molecules may be used to identify mucleic acid sequences which encode CCYPR. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding CCYPR, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the CCYPR encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:55-108 or from genomic sequences including promoters, enhancers, and introns of the CCYPR gene.

Means for producing specific hybridization probes for DNAs encoding CCYPR include the

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cloning of polynucleotide sequences encoding CCYPR or CCYPR derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as <sup>32</sup>P or <sup>35</sup>S, or by enzymatic labels, such as of reporter groups, for example, by radionuclides such as <sup>32</sup>P or <sup>35</sup>S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding CCYPR may be used for the diagnosis of disorders

associated with expression of CCYPR. Examples of such disorders include, but are not limited to, an immune disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome

tubal disease, ovulatory defects, and endometriosis, perturbations of the menstrual cycle, polycystic 32 gonadal steroid hormones such as: in women, abnormal prolactin production, infertility, including adenoma of the adrenal cortex, hypertension associated with alkalosis; disorders associated with associated complications; disorders associated with the adrenals such as hyperplasia, carcinoma, or (chronic hypercalemia); pancreatic disorders such as Type I or Type II diabetes mellitus and with bacterial infection; disorders associated with hyperparathyroidism including Conn disease 30 disorders associated with hypothyroidism including goiter, myxedema, acute thyroiditis associated inappropriate antidiuretic hormone (ADH) secretion (SIADH) often caused by benign adenoma; trauma; disorders associated with hyperpituitarism including acromegaly, giantism, and syndrome of malformations, thrombosis, infections, immunological disorders, and complications due to head adenomas, infarction associated with pregnancy, hypophysectomy, aneutysms, vascular 57 disorders of the hypothalamus and pituitary resulting from lesions such as primary brain tumors, disorders of immune cell activation; a cell signaling disorder including endocrine disorders such as anencephaly, craniorachisis, congenital glaucoma, cataract, sensorineural hearing loss, and hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spina bifida, neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, 70 myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' disorder such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a developmental extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, purpura, ulcerative colitis, uveitis, Wemer syndrome, complications of cancer, hemodialysis, and systemic lupus erythematosus, systemic scletosis, primary thrombocythemia, thrombocytopenic Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, myelofibrosis, osteoarthrius, osteoporosis, pancreatius, polycythemia vera, polymyosius, psoriasis, disorder (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, mixed connective tissue Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal lymphocytotoxins, etythroblastosis fetalis, etythema nodosum, atrophic gastritis, glomerulonephritis, dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with (APECED), bronchius, bursius, cholecystius, cirrhosis, contact dermatius, Crohn's disease, atopic autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis,

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detect aftered CCYPR expression. Such qualitative or quantitative methods are well known in the art. pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, thymus, thyroid, and uterus. The polymucleotide sequences encoding CCYPR may be used in Southern lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, ргітагу thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue impotence, carcinoma of the male breast, and gynecomastia; and a cell proliferative disorder such as cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, receptors, syndrome of 5 a-reductase, a disruption of spermatogenesis, abnormal sperm physiology, associated with Leydig cell tumors, androgen resistance associated with absence of androgen men, Leydig cell deficiency, male climacteric phase, germinal cell aplasia, hypergonadal disorders breast cancer, and fibrocystic breast disease; and, in post-menopausal women, osteoporosis; and, in gonadotropin deficiency, amenorrhea, galactorrhea, hermaphroditism, hirsutism and virilization, fibroid, autoimmune disorders, an ectopic pregnancy, teratogenesis, hyperprolactinemia, isolated ovarian disease, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine

detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding CCYPR may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control indicates the presence of altered levels of nucleotide sequences encoding CCYPR in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In a particular aspect, the nucleotide sequences encoding CCYPR may be useful in assays that

In order to provide a basis for the diagnosis of a disorder associated with expression of cCYPR, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding CCYPR, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified

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polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

Once the presence of a disorder is established and a treatment protocol is initiated,

overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or

Additional diagnostic uses for oligonucleotides designed from the sequences encoding CCYPR may involve the use of PCR. These oligoners may be chemically synthesized, generated enzymatically, or produced in vito. Oligomers will preferably contain a fragment of a polynucleotide encoding CCYPR, or a fragment of a polynucleotide complementary to the polynucleotide encoding CCYPR, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

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In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences

encoding CCYPR may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding CCYPR are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences are detectable and tertiary structures of PCR products in single-stranded form, and these differences are detectable and tertiary structures of PCR products in single-stranded form, and these differences are detectable fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual

overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of CCYPR include radiolabeling or

biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the

polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript where to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor profiles of therapeutic agents in the treatment of disease. In particular, this information may be used activities of therapeutic agents in the treatment of disease. In particular, this information may be used activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective the develop and monitor the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient of a patient at order to select the most appropriate and effective the display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

be used as elements on a microarray. The microarray may be used to monitor or measure proteinprotein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to

generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of

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transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies,

or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitto, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitto model systems and preclinical evaluation of

gene sequences. important and desirable in toxicological screening using toxicant signatures to include all expressed February 29, 2000, available at http://www.niehs.nih.gov/oc/news/toxchip.htm.) Therefore, it is example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not after treatment with different compounds. While the assignment of gene function to elements of a rest of the expression data. The normalization procedure is useful for comparison of expression data compounds are important as well, as the levels of expression of these genes are used to normalize the provides the highest quality signature. Even genes whose expression is not altered by any tested from a large number of genes and gene families. Ideally, a genome-wide measurement of expression These fingerprints or signatures are most useful and refined when they contain expression information signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. Toxicol, Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity compounds. All compounds induce characteristic gene expression patterns, frequently termed pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental

containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated

biological sample are hybridized with one or more probes specific to the polynucleotides of the

present invention, so that transcript levels corresponding to the polynucleotides of the present

invention may be quantified. The transcript levels in the treated biological sample are compared with

are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present

Another particular embodiment relates to the use of the polypeptide sequences of the present

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In one embodiment, the toxicity of a test compound is assessed by treating a biological sample

and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of CCYPR expression. In one embodiment, the antibodies are used as elements on a microarray, A proteomic profile may also be generated using antibodies specific for CCYPR to quantify the some cases, further sequence data may be obtained for definitive protein identification. at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. spot density related to the treatment. The proteins in the spots are partially sequenced using, for untreated with a test compound or therapeutic agent, are compared to identify any changes in protein positioned protein spots from different samples, for example, from biological samples either treated or generally proportional to the level of the protein in the sample. The optical densities of equivalently such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, supra). The proteins are isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzed by quantifying the number of expressed proteins and their relative abundance under given can be subjected individually to further analysis. Proteome expression patterns, or profiles, are pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global

levels of CCYPR expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) Anal. Biochem. 270:103-111; Mendoze, L.G. et al. (1999) Biotechniques 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or aminomethods known in the art, for example, by reacting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should

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be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) Electrophoresis 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological

sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the present invention. In another embodiment, the toxicity of a test compound is assessed by treating a biological

sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g.,

Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding CCYPR may be used

to generate hybridization probes useful in mapping the naturally occurring genomic sequences. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a multi-gene family may potentially cause undesired cross hybridization during chromosomas (BACs), bacterial artificial chromosomes (BACs), bacterial artificial chromosomes (BACs), bacterial PI constructions, or single chromosome constructions, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., particular chromosome region or restriction fragment length polymorphism (RFLP).

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map

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data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding CCYPR on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as

linkage analysis using established chromosomal markers, may be used for extending genetic maps.

Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., asti, R.A. et al. (1988) Nature 336:5777-580.) The nucleotide sequence of the instant invention may be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between CCYPR and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds

In another embodiment of the invention, CCYPR, its catalytic or immunogenic fragments, or

having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with CCYPR, or fragments thereof, and washed. Bound CCYPR is then detected by methods well known in the art. Purified CCYPR can

also be coated directly onto plates for use in the aforementioned drug screening techniques.

Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding CCYPR specifically compete with a test compound for binding CCYPR. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with CCYPR.

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In additional embodiments, the nucleotide sequences which encode CCYPR may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on

properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding

description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder

of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/145,075, U.S. Ser. No. 60/153,129, and U.S. Ser. No. 60/164,647, are

EXYMPLES

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues

#### I. Construction of cDNA Libraries

hereby expressly incorporated by reference.

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were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA

purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA

libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units objective deprecedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units objective deprecedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units objective deprecedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units objective deprecedures or similar methods from in the art. (See, e.g., Ausubel, 1997, supra, units appropriate restriction was initiated us double stranded cDNA, and the cDNA was size-selected (300-1000 pp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g.,

(Invitrogen, Carlsbad CA), or pIMCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5a, DH10B, or ElectroMAX DH10B from Life Technologies.

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIACEN. Following precipitation, plasmids were resuspended in 0.1 ml of

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using

PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows.

## III. Sequencing and Analysis

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(Labsystems Oy, Helsinki, Finland).

Isolation of cDNA Clones

distilled water and stored, with or without lyophilization, at 4°C.

Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI separation of cDNA sequencing reactions of labeled polynucleotides were carried out using the MECABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or using the MECABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some software; or other sequences analysis systems known in the art. Reading frames within the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

Of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed and analyzed.

using a combination of software programs, which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions,

references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate two sequences. Sequences were analyzed using MACDNASIS PRO software (Hitachi Software two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software polypeptide sequences). Sequences were geneated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and poly A sequences

and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Pered, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were subsequently analyzed by querying against databases such as the polynucleotide sequences were subsequently analyzed by querying against databases such as the and these full length sequences were subsequently analyzed by querying against databases such as the polynucleotide sequences were subsequently analyzed by querying against databases such as the metalistic approach which analyzes consensus primary structures of gene families. (See, e.g., probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g.,

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:55-108. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, <u>supra</u>, ch. 7; Ausubel, 1995, particular cell type or tissue have been bound. (See, e.g., Sambrook, <u>supra</u>, ch. 7; Ausubel, 1995,

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Analogous computer techniques applying BLAST were used to search for identical or related

molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

BLAST Score x Percent Identity
5 x minimum {length(Seq. 1), length(Seq. 2)}

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which methods are reported as a percentage distribution of libraries in which it is product score of northern analyses are reported as a percentage distribution of libraries in which

the transcript encoding CCYPR occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table

# Chromosomal Mapping of CCYPR Encoding Polynucleotides

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sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:55-108 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available

The cDNA sequences which were used to assemble SEQ ID NO:55-108 were compared with

from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID MO:, to that map location.

The genetic map locations of SEQ ID MO:71, SEQ ID MO:73, SEQ ID MO:73, SEQ ID MO:74, SEQ ID MO:74, SEQ ID MO:75, SEQ ID MO:76, SEQ ID MO:77, SEQ ID MO:77, SEQ ID MO:70, snd SEQ ID MO:70, SEQ ID MO:7

# VI. Extension of CCYPR Encoding Polynucleotides

disease genes map within or in proximity to the intervals indicated above.

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The full length nucleic scid sequences of SEQ ID MO:55-108 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to annelating the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

site (http://www.ncbi.nlm.nih.gov/genemap/), can be employed to determine if previously identified

was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction

Selected human cDNA libraries were used to extend the sequence. If more than one extension

was performed in 96-well plates using the PTC-200 thermal cyclet (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing  $Mg^{2+}$ , (MH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, and  $\beta$ -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme

(Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times;

Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN

quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates,

digested with CviJI cholers virus endonuclesse (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DMA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were plates and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were plates and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were plates and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were plates and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were plates and cultured overnight at 37°C in 384-well plates in LB/2x and transfer the colonies were plates and tra

carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham

Pharmacia Biotech) and Pfu DMA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DMA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DMA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle

sequencing reaction telt (PE Biosystems).

In like manner, the polynucleotide sequences of SEQ ID NO:555-108 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such

Hybridization probes derived from SEQ ID MO:55-108 are employed to screen cDMAs,

extension, and an appropriate genomic library.

## VII. Labeling and Use of Individual Hybridization Probes

genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base

5 pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments.

Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 µCi of [γ-³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston WA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10² counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of buman genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xbs I, or pyuu II (DuPont NEW).

The DNA from each digest is fractionated on a 0.7% agarose get and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

The linkage or synthesis of array elements upon a microarray can be achieved utilizing

#### 20 VIII. Microarrays

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(.16-72:31.)

photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), supra). Suggested analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol.

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array

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detail below. the microarray may be assessed. In one embodiment, microarray preparation and usage is described in complementarity and the relative abundance of each polynucleotide which hybridizes to an element on desorbtion and mass spectrometry may be used for detection of hybridization. The degree of fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser After hybridization, nonhybridized nucleotides from the biological sample are removed, and a biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the

#### Tissue or Cell Sample Preparation

resuspended in 14 µl 5X SSC/0.2% SDS. then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. 07 incubated for 20 minutes at 85 °C to the stop the reaction and degrade the RNA. Samples are purified with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one GEMBRIGHT kits (Incyte). Specific control poly(A)\* RNAs are synthesized by in vitto transcription transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)\* RNA with SI dCTP, 40 µM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse strand buffer, 0.03 units/µl RNase inhibitor, 500 µM dATP, 500 µM dGTP, 40 µM reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/µl oligo-(dT) primer (21mer), 1X first poly(A) RUA is purified using the oligo-(dT) cellulose method. Each poly(A) RUA sample is Total RNA is isolated from ussue samples using the guanidinium thiocyanate method and

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Biotech). pg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia 30 amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses Sequences of the present invention are used to generate array elements. Each array element is

Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water Purified array elements are immobilized on polymer-coated glass slides. Glass microscope

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coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. I µl of the array element DNA, at an average concentration of 100 ng/µl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALIMKER UV-crosslinker (Stratagene).

Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in

0.2% SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 µl of sample mixture consisting of 0.2 µg each of Cy3 and

Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm<sup>2</sup> coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microacope slide. The chamber is kept at 100% humidity internally by the addition of 140 µl of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 20 °C), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide

resolution of 20 micrometers.

Detection

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Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater MI) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital anotophore.

(A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot

is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

### 20 IX. Complementary Polynucleotides

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Sequences complementary to the CCYPR-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring CCYPR. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of CCYPR. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent designed to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the CCYPR-encoding transcript.

# X. Expression of CCYPR is achieved using bacterial or virus-based expression

systems. For expression of CCYPR in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the trp-lac (tac) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the lac operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3).

Antibiotic resistant bacteria express CCYPR upon induction with isopropyl beta-Dthiogalactopyranoside (IPTG). Expression of CCYPR in eukaryotic cells is achieved by infecting insect
or mammalian cell lines with recombinant <u>Autographica californica</u> nuclear polyhedrosis virus
(AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is
replaced with cDNA encoding CCYPR by either homologous recombination or bacterial-mediated
transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong
polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to
infect <u>Spodoptera frugiperda</u> (Sf9) insect cells in most cases, or human hepatocytes, in some cases.

Infect <u>Spodoptera frugiperda</u> (Sf9) insect cells in most cases, or human hepatocytes, in some cases.

al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther.

7:1937-1945.)

In most expression systems, CCYPR is synthesized as a fusion protein with, e.g., glutathione 5transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step,
affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton
glutathione under conditions that maintain protein activity and antigenicity (Ameraham Pharmacia
Biotech). Following purification, the GST moiety can be proteolytically cleaved from CCYPR at
specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification
using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins
(QIACEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra,
ch. 10 and 16). Purified CCYPR obtained by these methods can be used directly in the assays shown in

# XI. Demonstration of CCYPR Activity

synthesis in Swiss mouse 3T3 cells. A plasmid containing polynucleotides encoding CCYPR is transfected into quiescent 3T3 cultured cells using methods well known in the art. The transferred transfected cells are then incubated in the presence of [3H]thymidine, a radioactive DNA precursor.

Where applicable, varying amounts of CCYPR ligand are added to the transfected cells. Incorporation of [3H]thymidine into acid-precipitable DNA is measured over an appropriate time interval, and the amount incorporated is directly proportional to the amount of newly synthesized DNA and CCYPR amount incorporated is directly proportional to the amount of newly synthesized DNA and CCYPR

## XII. Functional Assays

Examples XI and XV.

activity.

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CCYPR function is assessed by expressing the sequences encoding CCYPR at physiologically

An assay for CCYPR activity measures cell proliferation as the amount of newly initiated DNA

regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; downςι changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in fluorescent molecules that diagnose events preceding or coincident with cell death. These events include apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-10 recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the marker protein are co-transfected. Expression of a marker protein provides a means to distinguish formulations or electroporation. 1-2  $\mu g$  of an additional plasmid containing sequences encoding a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression

(1994) Flow Cytometry, Oxford, New York NY.

The influence of CCYPR on gene expression can be assessed using highly purified populations

expression of cell surface and intracellular proteins as measured by the binding of fluorescein-conjugated and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated

Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G.

of cells transfected with sequences encoding CCYPR and either CD64 or CD64-GFP. CD64 and DD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding CCYPR and other genes of interest can be analyzed by northern analysis or microarray techniques.

## KIII. Production of CCYPR Specific Antibodies

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CCYPR substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the CCYPR amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is

synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, <u>supra</u>, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A

peptide synthesizer (PE Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, <u>supra.</u>) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-CCYPR activity by, for example, binding the peptide or CCYPR to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIV. Purification of Naturally Occurring CCYPR Using Specific Antibodies Naturally occurring or recombinant CCYPR is substantially purified by immunoaffinity

chromatography using antibodies specific for CCYPR. An immunoaffinity column is constructed by covalently coupling anti-CCYPR antibody to an activated chromatographic resin, such as CMBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is

blocked and washed according to the manufacturer's instructions.

Media containing CCYPR are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of CCYPR (e.g., high ionic strength

washed under conditions that allow the preferential absorbance of CCYPR (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/CCYPR binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such

XV. Identification of Molecules Which Interact with CCYPR

as urea or thiocyanate ion), and CCYPR is collected.

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CCYPR, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem J. 133;529-539.) Candidate molecules and any wells with labeled CCYPR complex are assayed. Data obtained using different concentrations and any wells with labeled CCYPR complex are assayed. Data obtained using different concentrations of CCYPR are used to calculate values for the number, affinity, and association of CCYPR with the candidate molecules.

Alternatively, molecules interacting with CCYPR are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, Nature 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

CCYPR may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT)

which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent

No. 6,057,101).

claims.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention.

Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments.

Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following to those skilled in molecular biology or related fields are intended to be within the scope of the following

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13	. 12	11	10	9	80	7	6	ហ	4	ω	2	1	Polypeptide SEQ ID NO:
67	66	65	64	63	62	61	60	59	58	57	56	55	Nucleotide SEQ ID NO:
3500375	3215187	2686765	2049176	1988468	1887228	1752768	1577739	1558289	1416289	1305252	1210462	116462	Clone ID
PROSTUT13	TESTNOT07	LUNGNOT23	LIVRFET02	LUNGAST01	BLADTUT07	LIVRTUT01	LNODNOT03	SPLNNOT04	BRAINOT12	PLACNOT02	BRSTNOT02	KIDNNOT01	Library
860585R1 (BRAITUT03), 1318501F1 (BLADNOT04), 1419126F1 (KIDNNOT09), 1483246F6 (CORPNOT02), 2238114T6 (PANCTUT02), 2272329H1 (PROSNON01), 3209746F7 (BLADNOT08), 3403213H1 (ESOGNOT03), 4176619H1 (BRAINOT22), 4614606H1 (BRAYDIT01)	151135R6 (FIBRAGT01), 3215187F6 (TESTNOT07), 3215187H1 (TESTNOT07)	1502858F6 (BRAITUT07), 1956694X315D1 (CONNNOT01), 2022628X307D1 (CONNNOT01), 2686765F6 (LUNGNOT23), 2686765H1 (LUNGNOT23), 2864555H1 (KIDNNOT20), 2887609F6 (SINJNOT02), 3381980H1 (ESOGNOT04)	2049176H1 (LIVRFET02), 2049176T6 (LIVRFET02), 2049176X321D1 (LIVRFET02)	072147R6 (THP1PEB01), 496297H1 (HNT2NOT01), 1362109F6 (LUNGNOT12), 1726095F6 (PROSNOT14), 1726095T6 (PROSNOT14), 1988468H1 (LUNGAST01), 1988468T6 (LUNGAST01), 2232471F6 (PROSNOT16)	080294F1 (SYNORAB01), 140055F1 (TLYMNOR01), 285207X42 (EOSIHET02), 516882R6 (MMLR1DT01), 1217892T1 (NEUTGMT01), 1887228H1 (BLADTUT07), 4323029H1 (TLYMUNT01)	2588 6 (PR 175 6 (LI	-4-	1558289H1 (SPLNNOT04), 1852450T6 (LUNGFET03), 2396092F6 (THP1AZT01), 2593267F6 (LUNGNOT22), 2632784F6 (COLNTUT15	752 1 ( ITU	794067R6 (OVARNOTO3), 871989R1 (LUNGASTO1), 1235253F1 (LUNGFETO3), 1305252F6 (PLACNOTO2), 1305252H1 (PLACNOTO2), 1703258T6.comp (DUODNOTO2), 2678307H1.comp (OVARTUTO7), 3221088H1.comp (COLNNONO3), 3647280H1 (ENDINOTO1)	STNOT02), 2378362H1	116462H1 (KIDNNOT01), 116462R1 (KIDNNOT01), 116462X304D1 (KIDNNOT01), 1500439F6 (SINTBST01), 2369977F6 (ADRENOT07)	Fragments

Table 1 (cont.)

27	26	25	24	23	22	21	20	19	18	17	16	15	14	Polypeptide SEQ ID NO:
81	80	79	78	77	76	75	74	73	72	71	70	69	68	Nucleotide SEQ ID NO:
1398816	926810	259983	035102	017900	5664154	2800717	2553926	1655123	1638819	1511488	058336	5218248	5080410	Clone ID
BRAITUT08	BRAINOT04	HNT2RAT01	HUVENOB01	HUVELPB01	BRAUNOT01	PENCNOT01	THYMNOT03	PROSTUT08	UTRSNOT06	LUNGNOT14	MUSCNOT01	BRSTNOT35	LNODNOT11	Library
056398F1 (FIBRNOT01), 1252138F2 (LUNGFET03), 1294556T1 (PGANNOT03), 1398816H1 (BRAITUT08), 1545328R1 (PROSTUT04)	926810H1 (BRAINOTO4), 3490378T6 (EPIGNOTO1), 4774848H1 (BRAQNOTO1), SBIA01080D1, SBIA04006D1, SBIA02273D1, SBIA01121D1	259131R1 (HNT2RAT01), 259983H1 (HNT2RAT01), 268205R1 (HNT2NOT01), 1305726F1 (PLACNOT02)	035102H1 (HUVENOB01), 077722R1 (SYNORAB01), 995133H1 (KIDNTUT01), 1356968T6 (LUNGNOT09), 1963135R6 (BRSTNOT04), 2659921F6 (LUNGTUT09), 3110603H1 (BRSTNOT17)	017900H1 (HUVELPB01), 092858F1 (HYPONOB01), 1353543F1 (LATRTUT02), 1353543F6 (LATRTUT02), 1428464F1 (SINTBST01), g1616429	181534F1 (PLACNOB01), SCHA00262V1		403261F1 (TMLR3DT01), 1869739F6 (SKINBIT01), 2197242T6 (SPLNFET02), 2553926H1 (THYMNOT03), 2553956T6 (THYMNOT03), 3935528H1 (PROSTUT09), 5263918F6 (CONDTUT02)	1271351F1 (TESTTUT02), 1353234F1 (LATRTUT02), 1655123H1 (PROSTUT08), 2132186R6 (OVARNOT03), 3296525H1 (TLYJINT01), 3354010H1 (PROSNOT28), 3741838F6 (MENTNOT01), 3741838T6 (MENTNOT01), SXAF03528V1	1282638T1 (COLNNOT16), 1638819F6 (UTRSNOT06), 1638819H1 (UTRSNOT06), 3597071H1 (FIBPNOT01), SBRA03813D1, SBRA03785D1	1436265F1 (PANCNOT08), 1511488H1 (LUNGNOT14), 1511488T6 (LUNGNOT14), 1850020F6 (LUNGFET03)	058336H1 (MUSCNOT01), 058336T6 (MUSCNOT01), g2206766, g2069225	1808748X15C1 (PROSTUT12), 1808748X16C1 (PROSTUT12), 3391884H1 (LUNGNOT28)	1270372X300D1 (BRAINOT09), 3460603H1 (293TF1T01), 5080410H1 (LNODNOT11)	Fragments

Table I (cont.)

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37		35	34	u u	32	u 1	30	29	28	Polypeptide SEQ ID NO:
91	90	89	88	87	86	85	84	83	82	Nucleotide SEQ ID NO:
1980010	1868749	1851534	1806850	1806454	1708229	1678765	1620092	1514559	1496820	Clone ID
LUNGTUT03	SKINBIT01	LUNGFET03	SINTNOT13	SINTNOT13	PROSNOT16	STOMFET01	BRAITUT13	PANCTUT01	PROSNON01	Library
こしのしにご	(BLADNOTO4), 1398330F1 (BRAITUTO8), 1), 1868749F6 (SKINBITO1), 1868749H1 (PROSNONO1), 2684670H1 (LUNGNOT23), 4), 4951533H2 (ENDVUNTO1), 5077673H1 (BRAINOT19)	<u>ه</u> _ ا	270548H1 (HNT2NOT01), 443885R1 (MPHGNOT03), 1257235F1 (MENITUT03), 1337438H1 (COLNNOT13), 1351820F1 (LATRTUT02), 1544066R1 (PROSTUT04), 1806850F6 (SINTNOT13), 1806850H1 (SINTNOT13), 1984108T6 (LUNGAST01), 2921419H1 (SININOT04), 3109392H1 (BRSTTUT15)	SIHET02), 821556R1 (KERANOT02), 16 1710552H1 (PROSNOT16), 1806454F6 INTNOT13), 2526283H1 (BRAITUT21),	388493R1 (THYMNOTO2), 1503519F1 (BRAITUTO7), 1708229H1 (PROSNOT16), 1725267F6 (PROSNOT14), 3089258F6 (HEADNOTOA)	1678765H1 (STOMFETO1), 2 (TONSNOTO3), 4180591H1 ( 4349212H1 (TLYMTXTO1), 4 (OVARNONO3), 5332272H1 (	(BRAITUT13), 1620092H1 ( 1), 1843815R6 (COLNNOT08)	155768H1 (THP1PLB02), 1229952H1 (BRAITUT01), 1337018X11 (COLNNOT13), 1360361H1 (LUNGNOT12), 1365811H1 (SCORNON02), 1514559F6 (PANCTUT01), 1514559H1 (PANCTUT01)	996673H1 (KIDNTUT01), 1496820H1 (PROSNONO1), 2368484F6 (ADRENOT07), 3071781X303D1 (UTRSNOR01), 3071781X307B1 (UTRSNOR01), 3071781X316D3 (UTRSNOR01)	Fragments

Table 1 (cont.)

				L					
46	45	44	43	42	41	40	39	o	Polypeptide SEQ ID NO:
100	99	98	97	96	95	94	93	94	Nucleotide SEQ ID NO:
3520701	3082014	2959521	2797839	2683225	2668536	2456494	2359526	4234034	Clone ID
LUNGNON03	BRAIUNT01	ADRENOT09	NPOLNOT01	SINIUCTOI	ESOGTUT02	ENDANOT01	LUNGFET05	OVARIOTOL	Library
971201H1 (MUSCNOT02), 1544657R6 (PROSTUT04), 1545570H1 (PROSTUT04), 1671030F6 (BMARNOT03), 1671030T6 (BMARNOT03), 2605263F6 (LUNGTUT07), 3520701H1 (LUNGNON03), 3520701R6 (LUNGNON03)	182588H1 (PLACNOBO1), 645276R6 (BRSTTUT02), 1497811F1 (SINTBST01), 2051505F6 (LIVRFET02), 3082014H1 (BRAIUNT01), 3464112F6 (293TF2T01), 4603079H1 (BRSTNOT07)	CORNNOTO1), 01 ), 167505H1 (1 ), 167505H1 (1 9, 2641117H1 ), 2641117H1 (ADRENOTO9), 3 ), 3138371H1 (ADRETUTO7), 3 (ADRETUTO7), 3	(ERANOT01), , 1218533H1 (THP1NOT03), , 3350118H1 (TESTTUT03), , 5524886H1	196443R6 (KIDNNOTO2), 1243440R6 (LUNGNOTO3), 1604540F6 (LUNGNOT15), 2072837H1 (ISLTNOTO1), 2683225F6 (SINIUCTO1), 2683225H1 (SINIUCTO1), 3647874H1 (ENDINOTO1), 4029178H1 (BRAINOT23)	(PANCTUT01), 1 ), 1721443F6 ( (PENCNOT05),	PROSNOT18), 245 , 3618339H1 (EP	(LUNGFET05), ), 2654667T6	(SYNORATO5), 1418710F1 (KIDNNOTO9), 1264124H1 (SYNORATO5), 1418710F1 (KIDNNOTO9), 1697570T6 (BLADTUTO5), 1874051F6 (LEUKNOTO2), 2187960T6 (PROSNOT26), 2259032H1 (OVARTUTO1), 2259032R6 (OVARTUTO1), 3406237H1 (ESOGNOTO3), 3441729H1 (PENCNOTO6), 3555764H1 (LUNGNOT31), 3728010H1 (SMCCNONO3), 3813639H1 (TONSNOTO3), 4031501H1 (BRAINOT23), 4274704H1 (PROSTMTO1), 4602450H1 (BRSTNOTO7), g3327183	S

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
47	101	4184320	BRADDIT02	2156956F6 (BRAINOTO9), 4184253F6 (BRABDIRO1), 4184253T6 (BRABDIRO1), 4184320H1 (BRADDITO2), 4252542F6 (BRADDIRO1)
48	102	4764233	PLACNOT05	(PLACNOTOS), 5634642H1 (PLACFERO1),
49	103	4817352	HELATXT03	(BLADNOTO1), 426993T6 (BLADNOTO1), 4:
50	104	5040573	COLHTUT01	(PROSNOT14), 1859337F6 (PROSNOT18), 2
				(ADRETUT07), 3322214H1 (PTHYNOT03), 4601227H1 (BRSTNOT07), 4885408H1 (COLHTUT01)
51	105	5627029	PLACFER01	967988R1 (BRSTNOT05), 1534642T6 (SPLNNOT04), 1700904F6 (BLADTUT05), 1846971R6 (COLNNOT09), 2112727R6 (BRAITUT03),
				3), 3439165F6 (PENCNOTO6), 3604622H1 (
52	106	5678487	293TF2T01	12587876 (MENITUTO3), 1522008F1 (BLADTUTO4), 1597992F6   (BLADNOTO3), 2057679H1 (BEPINOTO1), 2411504H1 (BSTMNONO2),
				(THYRNOTOB), 2739089F6 (OVARNOTO9),
				3254971R6 (OVARTUN01), 3487616H1 (EPIGNOT01), 5678487H1
53	107	5682976	BRAENOTO2	150492H1 (IVENNOTO1) ROSSAGIRI (PROGNOTOG) ROSSGGB1
				02), 1667502F6 (BMARNOT
				(BONRTUTO1), 2896448H1 (KIDNTUT14), 3141553H1 (SMCCNOTO2),
				7), 5682976H1 (BRAENOTO2), 5546853H1
54	108	5992432	FTUBTUT02	
				T19), 3592787H1 (293TF5T01), 5992432H1
				8121012

l'able 2

	C. SUATAWAT					
BLAST_GenBank	mark-5 (g410/015)			S141 S142 T152		
MOTIFS	Posterior end				173	6
	sapiens				·	
BLAST_GenBank	[23860093] H					
MOTIFS	Differentiation		N76	T34 S103 S5 T136	184	vi
BLAST_GenBank	Mus musculus			S246 Y189		
BLIMPS_PFAM	protein (g5814404)	protein: E96-N297		S127 S176 T207		
MOTIFS	Germ cell-less	Germ cell-less	N74		297	4
	sapiens			S298		
	(g2829208) H.		N306	S369 S64 S247		
BLAST_GenBank	suppressor p33ING1		N203 N288	T156 S292 S349		
MOTIFS	Candidate tumor		N190 N191	S246 S415 T142	418	ω
		nucleolar protein P120: E26-G293				
		Proliferative cell				
BLAST_GenBank	fulgidus			S234 T337		
BLAST_DOMO	P120 (g2649749) A.	antigen: N117-K333		S165 S226 S230		
BLAST_PRODOM	nucleolar antigen	proliferating cell		T307 S88 S102		
MOTIFS	Proliferating cell	P120 nuclear		T39 S190 S268	340	2
		domain: M1-R99				
		transduction-related				
		GLGF signal				
		repeat: L8-R99				
BLAST_DOMO		Protein SH3 domain				
BLAST_PRODOM						
SPSCAN		Q33				
MOTIFS		Signal peptide: M1-	N15 N38	T10 S93	145	۲
Databases			Sites	Sites	Residues	ID NO:
Methods and	Sequences	Motifs and Domains	Glycosylation	Phosphorylation	Acid	tide SEQ
Analytical	Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-

		78			
11	10	9	ω	7	Polypep- tide SEQ ID NO:
533	S. U	270	463	591	Amino Acid Residues
\$227 \$412 \$505 \$7 \$17 \$65 T349 \$442 T29 \$72 \$89 \$358 \$442 T446 \$505 Y244	\$180 T49 T53 \$97 \$152 T201 \$210 \$23 \$97 T145 T216 \$225 \$228 T231 \$242 Y106 Y240		T237 S34 T67 T117 T125 S138 T288 T321 S328 S418 T80 S186 S190 S209 S210 T232 T288 S418 T441 S445 Y416	S582 T71 T208 S217 S339 T475 S493 T536 S45 S105 S153 T208 S305 S336 T578 Y93	Potential Phosphorylation Sites
		N64 N94 N147	N208	N374 N425 N534 N585	Potential Glycosylation Sites
TRE oncogene: R56- 1277	Polyposis locus TB2 homolog: G15-T117 Polyposis locus protein: V13-T117		Formin limb . deformity: M1-E335	Signal peptide M1- L64  TPR domain mitosis control E239-P356  TPR repeat V265-K516	Signature Sequences, Motifs and Domains
TRE oncogene- related protein (g2286196) <u>D.</u> melanogaster	Similar to polyposis locus protein 1 (9849238) H. sapiens	Early embryogenesis MRG1 protein (g2570051) M. musculus	Lymphocyte specific formin related protein (g4101720) M. musculus	Cell division cycle protein 23 homolog (g5541721) A. thaliana	Homologous Sequences
MOTIFS BLOCKS_DOMO BLAST_GenBank	MOTIFS BLAST_PRODOM BLAST_DOMO BLAST_GenBank	MOTIFS BLAST_GenBank	MOTIFS BLAST_PRODOM BLAST_DOMO BLAST_GenBank	MOTIFS SPSCAN HMMR_PFAM BLAST_DOMO BLAST_GenBank	Analytical Methods and Databases

Table 2 (cont.)

17	16	15	14	13	12	Polypep- tide SEQ ID NO:
162	168	199	165	531	160	Amino Acid Residues
S70 S85 T16 T28 T65 T80 T100 S127 Y111	S141 S55 S61 T79	S2 S21 S69 T102 S189	S3 T67 S104	S195 T196 S357 T45 S172 T199 S212 S322 S465 T495 T45 T241 S255 T279 T319 S328	S40	Potential Phosphorylation Sites
·	N77			N244 N401		Potential Glycosylation Sites
	Signal peptide M1-S61 H-Rev protein homolog P15-K166				Signal peptide: M1-A30  Transmembrane domain: A6-I29  Cornichon developmental protein: M1-S160	Signature Sequences, Motifs and Domains
g207250 growth and transformation dependent protein Rattus norvegicus	g3777529 retinoic acid receptor responder 3 Homo sapiens	Developmental protein DG1118 (g3789911) D. discoideum	Wolf-Hirschhorn syndrome candidate 2 protein (g3860187) H. sapiens	Cdc 73p (g632679) S. cerevisiae	nicho	Homologous Sequences
BLAST-GenBank	BLAST-GenBank SPSCAN BLAST-PRODOM MOTIFS	MOTIFS BLAST_GenBank	MOTIFS BLAST_GenBank	MOTIFS BLAST_GenBank	MOTIFS SPSCAN HMMR BLAST_PRODOM BLAST_DOMO BLAST_GenBank	Analytical Methods and Databases

lable 2 (cont.)

BLAST-GenBank PROFILESCAN MOTIFS	LDOC-1 protein g3869127 (Homo sapiens) Nagasaki,K. et al. (1999) Cancer Lett. 140:227-234.	Biotin-requiring enzyme attachment site: L40-L90	·	S88 T20 T37	113	23
BLAST-GenBank MOTIFS BLAST-PRODOM	g4580592 brain expressed X- linked protein 2 Mus musculus	Prenyl group binding site (CAAX box) C125-P128 Ovarian granulosa cell 13.0 KD protein HGR74 N16-P128	N42	S3 S107	128	22
BLAST-GenBank	g455719 Activated c-raf oncogenic fusion protein homolog Homo sapiens		N190 N311	\$122 \$235 T60 \$192 \$203 \$204 \$218 \$226 \$307 T313 \$332 \$366 \$370 T375 T402 \$409 \$89 \$118 \$241 \$284 T360 \$399	425	21
BLAST-GenBank SPSCAN MOTIFS	g3901272 ZW10 interactor Zwint Homo sapiens	Signal peptide M1-L28		T129 T6 T102 T119 T181 S250 S46 T72 T84 S262	280	20
BLAST-GenBank SPSCAN BLAST-PRODOM MOTIFS	91322234 OS-9 precursor Homo sapiens	Signal peptide M1-G29 OS-9 precursor L54-E281		T394 T85 S86 S219 S225 T230 S298 T299 T472 S114 S200 T273 S371 T407 T424 T431	483	19
BLAST-GenBank BLAST-PRODOM BLAST-DOMO MOTIFS	g2622903 cell division protein J Methanobacterium thermoauto- trophicum	Protein cell intergenic region FTSJ K25-K241	N26 N158	T209 S227 T243 T28 S223 S51 S136 S201	246	18
Analytical Methods and Databases	Homologous Sequences	Signature Sequences, Motifs and Domains	Potential Glycosylation Sites	Potential Phosphorylation Sites	Amino Acid Residues	Polypep- tide SEQ ID NO:

Table 2 (cont.)

			<u> </u>			
29	28	27	26	25	24	Polypep- tide SEQ ID NO:
120	ພ ຫ	93	402	221	308	Amino Acid Residues
157	\$125 T42 \$43 \$85 \$212 \$283 \$314 T42 \$49 \$105 \$120 \$133 \$162 \$163 \$212 \$290	S11	T344 S39 S78 S109 S237 T269 S273 T376 T381 T383 S11 S49 T89 T344 S364	S145 S160 S217 S25 S31 S70 S85 T89 S153 S197 Y34	S95 T79 T98 S184 S246 S251 T55 S184 S226 S294 S300 Y127	Potential Phosphorylation Sites
	N145 N157 N191		N76 N107 N171 N362	N139	N77	Potential Glycosylation Sites
Cyclin-dependent kinase inhibitor: D7-P106, M1-N114	af-4 (FEL protein): S195-K353 E4-Q185			Annexin VI signature: L86-V95 Sushi domain: T165-C174	Melanoma antigen gene (MAGE) family: M1-Q200, H205-D283, D91-A287	Signature Sequences, Motifs and Domains
Cyclin dependent kinase inhibitor CIP1 g2276312 (Homo sapiens)	AF5q31 protein g6601438 (Homo sapiens)	Hypoxia inducible gene-1 g4929330 (Homo sapiens)	Paraneoplastic cancer-testis-brain antigen g6179740 (Homo sapiens)	Teratocarcinoma expressed gene Tera g1575505 (Mus musculus)	Breast cancer associated gene 1 g4928044 (Homo sapiens) Lurquin,C. et al. (1997) Genomics 46:397-408.	Homologous Sequences
BLAST-GenBank BLAST-PRODOM BLAST-DOMO MOTIFS	BLAST-GenBank BLAST_PRODOM BLAST-DOMO MOTIFS	BLAST-GenBank MOTIFS	BLAST-GenBank MOTIFS	BLAST-GenBank BLIMPS-PRINTS BLIMPS-PFAM MOTIFS	BLAST-GenBank BLAST-PRODOM HMMER-PFAM BLAST-DOMO MOTIFS	Analytical Methods and Databases

Table 2 (cont.)

Biol Cell 9:29-46.					
M.Winey (1998) Mol					
F.C.Luca and					
g3947877					
. ×.	L74-I230				· <del>-</del>
protein	kinase Binder MPS1:		S169		-
Putative	Serine-Threonine	N90	S7 T104 T154	268	32
-			S771 Y856		
			S671 S675 T706		
			S309 S423 S592		
			T732 S759 S188		
			S641 S642 S725		
			S499 T531 S627		
(1993) Mol. Gen.		•	S394 S460 S491		_
Irie, K. et al.			S346 S353 S378		
cerevisiae)			S282 S313 T328		
(Saccharomyces		-	S261 S266 S280		
g218488			S223 S224 S240		
protein Smp2		N639 N883	T129 S162 S203		
Replication		N107 N238	S603 T51 S109	933	31
Cell 50:1081-1089					
F.Cuzin (1987)					
N.Glaichenhaus and		-			
norvegicus)					
700	1			-	
g207250	193~1110				
dependent protein	domain:				
Transformation	Transmembrane		S15 S64	144	30
_		Sites	Sites	Residues	ID NO:
Sequences	Motifs and Domains	Glycosylation	Phosphorylation	Acid	tide SEQ
Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-

Table 2 (cont.)

36	35	ω Aı	33	Polypep- tide SEQ ID NO:
495	228	565	337	Amino Acid Residues
S451 S152 S365 S478 S108 S171 S181 T192 T347 T409 S435 Y86 Y111 Y203	S200 T47 T62 S78 S107 S188 S192 S206 S200 S205 S213	T17 S34 S61 S66 T138 T142 S174 T238 S245 S265 S436 S466 S527 S106 S205 S218 S258 T297 S314 T325 S463 T470 Y460	T29 S236 T44 T238	Potential Phosphorylation Sites
·	N36 N94 N225	N347 N386 N506		Potential Glycosylation Sites
		F-Box domain: H75-Y123, L82-N95 Disease resistance protein: G254-I270	Leucine zipper: L259-L280, L266-L287	Signature Sequences, Motifs and Domains
Malignant brain tumor protein 1(3)mbt g3811111 (Homo sapiens) Koga, H. et al. (1999) Oncogene 18:3799-3809.	Predicted WHSC1 protein (Wolf- Hirschhorn syndrome critical region 1) g4378022 (Homo sapiens) Stecc I. et al. (1998) Hum. Mol. Genet. 7:1071- 1082.	F-box protein FLR1 g7672734 (Homo sapiens)	DNA binding protein g184390 (Homo sapiens) Weitzel,J.N. et al. (1992) Genomics 14:309-319.	Homologous Sequences
BLAST-GenBank MOTIFS	BLAST-GenBank MOTIFS	BLAST-GenBank HMMER_PFAM BLIMPS-PRINTS MOTIFS	BLAST-GenBank MOTIFS	Analytical Methods and Databases

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Table 2 (cont.)

	16:2744-2755.					
	(1996) Mol. Cell Biol.			T780		
	Luke, M.M. et al.			T279 T527 S598		
	es pombe)			S796 S807 S93		
Ω.	(Schizosaccharomy			S719 S746 S753		
	g3426127			S437 S518 T523		
	phosphatase			T275 S412 S416	-	
MOTIFS	cycle dependent			T214 T240 S244		
BLAST-DOMO	putative cell	I92-Q364		T80 S171 S202		
BLAST-GenBank	Sap2 family	SAP:	N8 N210 N426	T532 S11 T23	.934	38
$\vdash$				S1220 Y631		
				T889 S940 S961		
	-			T696 S867 T883		
				T379 T389 T475		
				T169 S224 T352		
				S1249 T48 S94		
_				S1227 T1245		
				T1085 S1132		
				S997 S1049		
				S944 S959 S961		
				S834 T859 T915		
				T699 T729 S774		
_						
		L211-L232		T579 T626 T642	<u> </u>	
	(Homo sapiens)	Leucine zipper:		S313 T427 S467		
MOTIFS	g4337460	R1172-N1194	N1213 N1247	S95 S156 T298		
BLIMPS-PRINTS	related protein	S14 signature:	N345 N385	S10 S32 S33 T76		
BLAST-GenBank	Neuroblastoma	Ribosomal protein	N148 N152	T635 T769 S902	1336	37
Databases			Sites	Sites	Residues	ID NO:
Methods and	Sequences	Motifs and Domains	Glycosylation	Phosphorylation	Acid	tide SEQ
Analytical	Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-

Table 2 (cont.)

42 131 S78 T121	41 580 S324 S36 S550 S86 T119 T150 S329 S340	40 146 S61	39 515 T72 S122 S175 S272 S277 S30 T420 S422 T43 T79 S139 T189 S215 T316 S45 T486 Y13 Y383	tide SEQ Acid Phosphory ID NO: Residues Sites
1 T26	S36 S340 N190 S86 T109 T150 T226 S340		\$122 \$175 N16 N31 N115 2 \$277 \$305 3 \$422 T432 \$139 T189 5 T316 \$457 5 Y13 Y383	Phosphorylation Glycosylation Sites Sites
Presenilin: Q64-K75	Cyclin: H19-K262	Leucine zipper: L5-L26, L12-L33, L19-L40	Associated Protein: E65-R230 Leucine zipper: L234-L255	on Motifs and Domains
Cell growth regulator DRR1 g4322559 (Homo sapiens) G.Thomas and M.N.Hall (1997) Curr. Opin. Cell Biol. 9:782-787.	Cyclin K g3746549 (Homo sapiens) Edwards, M.C. et al. (1998) Mol. Cell Biol. 18:4291-4300.	LDOC1 g3869127 (Homo sapiens)	Metastasis associated gene g1008544 (Homo sapiens) Toh,Y. et al. (1995) Gene 159:97-104 Toh,Y, et al. (1994) J Biol. Chem. 269:22958-22963.	Sequences
BLAST-GenBank BLIMPS-PRINTS MOTIFS	BLAST-GenBank BLAST-PRODOM MOTIFS	BLAST-GenBank BLIMPS-PFAM MOTIFS	BLAST-GenBank BLAST-PRODOM BLIMPS-PRINTS MOTIFS	Methods and Databases

Table 2 (cont.)

<b>4</b> 5	44	43	Polypep- tide SEQ ID NO:
58 4	537	812	Amino Acid Residues
\$185 T324 \$343 T537 \$575 \$17 T102 \$128 T229 T374 \$412 T450	S505 T69 S138 S194 S310 S337 S356 T386 S485 S37 T45 T282	\$44 \$588 \$646 \$801 \$111 \$120 \$134 \$1140 \$148 \$150 \$181 \$1185 \$262 \$279 \$440 \$7477 \$497 \$7520 \$7542 \$7605 \$675 \$40 \$764 \$7311 \$7316 \$7319 \$7505 \$562 \$565 \$7566 \$7695 \$702 \$707 \$708 \$7739 \$7776 \$790 \$7277	Potential Phosphorylation Sites
N28	N122 N132 N147	N503 N618	Potential Glycosylation Sites
Cytochrome C motif: C283-T288 Metastasis- associated protein MTA1: R19-R143, D144-K321, G340-G483, P432-K555 Leucine zipper: L147-L168	Transmembrane domains: 1506-G532, V271-L290, W472-F490	NOL1/NOP2/fmu(sun) family signature: F454-G467, F300-K585, I388-M402, G410-G433, F454-G467, K507-L532, E189-M576 Proliferating Cell Nucleolar Antigen P120: M1-S134, E135- T311, F587-G805	Signature Sequences, Motifs and Domains
Metastasis associated gene g1008544 (Homo sapiens) Toh,Y. et al. (1995) Gene 159:97-104 Toh,Y. et al. (1994) J. Biol. Chem. 269:22958-22963.	Estrogen induced protein in breast cancer LIV-1 g1256001 (Homo sapiens)	Proliferating cell nuclear protein P120 g287723 (Homo sapiens)	Homologous Sequences
BLAST-GenBank BLAST-PRODOM MOTIFS	BLAST-GenBank HMMER MOTIFS	BLAST-GenBank BLAST-PRODOM BLAST-DOMO BLIMPS-BLOCKS MOTIFS HMMER-PFAM	Analytical Methods and Databases

**bCT/US00/19948** 

Table 2 (cont.)

	J.L.Maller (1995) Mol. Gen. Genet. 246:387-396.					
	g595380 (Xenopus laevis)			S368 Y350		
	catastrophe)			7 S3		
MOTIFS	prevents mitotic	A236-E402		546 S	-	
BLAST-DOMO	gene which			T413		
BLAST-GenBank	Mitotic regulator	XPMC2 (mitosis	,	T110 T159 S136	422	49
	182:689-698.					
	J. Exp. Med.					
	et al. (1995)		_			
	Van den Eynde, B.				•	
	(Homo sapiens)					
	GAGE-8 g3511023 ·				-	
MOTIFS	associated antigen		-			
BLAST-GenBank	Melanoma			T30 S2 T8	111	48
	58:1515-1520.					
	(1998) Cancer Res.					
	Duncan, L.M. et al.					
MOTIFS	(Mus musculus)	] G199-G255	_			
BLAST-PRODOM	g3047242	M1-R172,			•	
BLAST-GenBank	Melastatin	Melastatin:	N144	T9 T147 S237	255	47
		N308-E408		S52 S85 T93		
		P226-Y245,		S265 T315 S43		
		L24-R188,	-	T206 T235 S263		
MOTIFS		associated protein:		S19 S41 S205		
BLAST-PRODOM		MLO2 mitosis-	N275	S190 T301 S12	425	46
Databases			Sites	Sites	Residues	ID NO:
Methods and	Sequences	Motifs and Domains	Glycosylation	Phosphorylation	Acid	tide SEQ
Analytical	Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-
						0

able 2 (cont.)

				Т658 Ү459		
				S321 T568 S614		
				T20:		
	76:652-658.			T617 S693 S94		
	Int. J. Cancer			T482 T538 T581		
	al. (1998)			S335 S381 T464		
-	Scanlan, M.J. et			T231 T256 S325		
MOTIFS	(Homo sapiens)			T191 T192 S218		
BLAST-DOMO	g3170180			T121 T172 T177		
BLAST-PRODOM	antigen NY-CO-8	L680-L701		S20 T42 T114		_
BLAST-GenBank	Colon cancer	Leucine zipper:	N7 N49 N462	S100 T631 S8 T9	713	52
-				Y316 Y569 Y685		
·				T743 S789 Y102		
				T716 S730 S738		
-				S348 T398 T402		
				S89 S107 T123		
				S686 S3 S4 S65		
				S596 S598 T626		
				T466 S474 T562		
				S335 T392 S448		
				S265 T275 S321		
		L365-L386		T189 T235 S250		
MOTIFS		Leucine zipper:		S111 S119 T146 .		
SPSCAN	(Mus musculus)	M1-A25		S760 S48 S84		
BLAST-GenBank	SART-1 g4126469	Signal peptide:	N554 N665	S56 S448 T721	800	15
				S288 S326		
		K17-L347		S185 S218 S231		
	cerevisdiae)	control protein:		T64 T168 S180		
MOTIFS	(Saccharomyces	Cell division		S262 S307 T341		
BLAST-PRODOM	g550426	I361-L380, L24-L44		S127 S208 T210		
HMMER	CDC1	motifs:		T57 S59 T64		
BLAST-GenBank	Cell cycle protein	Transmembrane	N222 N260	S20 S21 T395	397	50
Databases			Sites	Sites	Residues	ID NO:
Methods and	Sequences	Motifs and Domains	Glycosylation	Phosphorylation	Acid	tide SEQ
Analytical	Homologous	Signature Sequences,	Potential	Potential	Amino	Polypep-

PCT/US00/19948

Table 2 (cont.)

Polypep-	Amino	Potential	Potential	Signature Sequences,	Homologous	Analytical
tide SEQ	Acid	Phosphorylation	Glycosylation	Motifs and Domains	Sequences	Methods and
ID NO:	Residues	Sites	Sites			Databases
53	880	S18 S68 T123	N60 N251 N338	MybI DNA-binding	homologous to	BLAST-GenBank
		T143 S159 T178	N514 N585	domain:	mouse gene PC326	BLAST-DOMO
		T286 S294 S327	N643	W808-I816	g458692	HMMER-PFAM
		S376 S388 T397		WD40 domains:	(Homo sapiens)	BLIMPS-PRINTS
		T403 S426 S438		L41-N79, K84-N124,	Bergsagel, P.L.	MOTIFS
		S474 S563 T587		T131-D170,	et al.	
		T634 T645 S659		G239-D281,	(1992)	
		S665 S677 S756		A771-S809,	Oncogene	
		S799 S809 T827		F157-T171	7:2059-2064.	
		S870 S82 T88		Acidic Serine		
		S99 T131 T165		Cluster Repeat:		
		S215 S253 S362		A423-R697		
		S487 T510 S525				
		S589 T593 S622				
54	855	T460 S8 S179	N552	Crooked neck protein	Predicted TPR	BLAST-GenBank
		S261 T288 T313		(RNA processing	domain protein	BLAST-PRODOM
		T377 T706 T719		associated, contains	G2315362	MOTIFS
		T755 S764 S803		TPR repeat):	(Caenorhabditis	
		S851 S34 S67		W398-V814	elegans)	
		T129 S190 S339			Zhang, K. et al.	
		T391 S483 S502		•	(1991)	
		S537 Y92			Genes Dev.	
					5:1080-1091.	

able 3

Table 3 (cont.)

	į	75			74				73				72			71		70			69					88			67			66	SEQ ID NO:	Nucleotide
	535-579	241-285			651-695			1066-1110	106-150				604-648			164-208		77-121			64-108					451-495		1136-1180	326-370			37-81	Fragments	Selected
	rointest	Reproductive (0.193) Cardiovascular	(0.161)	Reproductive (0.226) Cardiovascular	Hematopoietic/Immune (0.290)		Cardiovascular (0.114)	Nervous (0.202)	Reproductive (0.307)		Hematopoietic/Immune (0.128)	Gastrointestinal (0.149)	Reproductive (0.362)		Nervous (0.222)	Developmental (0.222)	Musculoskeletal (0.500)	Cardiovascular (0.500)	(0.140)	Nervous (0.174) Cardiovascular	Reproductive (0.233)	Urologic (0.125)	Hematopoietic/Immune (0.125)	(0.125)	Reproductive (0.312) Developmental	Nervous (0.312)	Hematopoietic/Immune (0.158)	Reproductive (0.237)	Nervous (0.237)	(0.250)	Dermatologic (0.250) Reproductive	Nervous (0.500)	(Fraction of Total)	Tissue Expression
Cell proliferation (0.169)	Inflammation/Trauma	- 1	Cell proliferation (0.230) Cancer (0.320)	(0.451)	Inflammation/Trauma	Cell proliferation (0.175)	(0.307)	Inflammation/Trauma	Cancer (0.482)	Cell proliferation (0.170)	(0.276)	Inflammation/Trauma	Cancer (0.426)	Trauma (0.222)	Cell proliferation (0.222)	Cancer (0.444)	Trauma (0.500)	Cancer (0.500)	Cell Proliferation (0.198)	Inflammation (0.279)	Cancer (0.477)			Cell Proliferation (0.312)	Inflammation (0.188)	Cancer (0.562)	Cell Proliferation (0.158)	Inflammation (0.316)	Cancer (0.395)			Inflammation (0.500)	Fraction of Total	Disease or Condition
		pINCY			PINCY				PINCY				PINCY		•	PINCY		PBLUESCRIPT			PINCY					PINCY			PINCY			pINCY		Vector

Table 3 (cont.)

	85	-		84				83						82			81			80			79			78			77				76	SEQ	Nucl
																				£														ID NO:	Nucleotide
	124-168			342-386				177-221						150-194			149-194			870-914			79-123			176-220			13-57			593-637	173-217	Fragments	Selected
a z	0 #	Z	<u>α</u> ;	R		<u> </u>		77	U			(F)	Ó	20	ရ	על	7	Ы	20	Z	D	_	N	6	777	Z	C	7	71			מכ			
Nervous (0.154) Gastrointestinal	Hematopoietic/Immune (0.308) Cardiovascular (0.154)	Nervous	Gastrointestinal (0.196)	Reproductive (0.252)	Nervous (0.128)	Hematopoietic/Immune (0.128)	Gastrointestinal (0.173)	Reproductive	Urologic (0.125)	Developmental (0.125)	Hematopoietic/Immune (0.125)	Endocrine (0.125)	Cardiovascular (0.125)	Reproductive (0.375)	Gastrointestinal (0.185)	Reproductive (0.201)	Nervous	Developmental	Reproductive (0.238)	Nervous (0.571)	Developmental (0.160)	Cardiovascular	Nervous	Gastrointestinal	Reproductive (0.235)	Nervous	Cardiovascular	Nervous (0.202)	Reproductive				Nervous	Fraction of	Tissue E
(0.154) ntestina	ietic/I scular	(0.161)	testina	tive (C	(0.128)	ietic/I	testina	tive (C	(0.125	ental (	ietic/I	le (0.12	scular	tive (C	testina	tive ((	(0.216)	l	tive (C	(0.571)	nental (	scular	(0.280)	testina	tive (	(0.279)	scular	(0.202)	tive (0.			tive (C	(0.513)		Expression
1 (0.154)	(0.154)		1 (0.19	252)		mmune (	1 (0.17	(0.199)	<u> </u>	0.125)	mmune (	5)	(0.125)	.375)	1 (0.18	.201)		(0.095)	).238)		0.160)	(0.160)		1 (0.147)	).235)		(0.140)		.241)			).167)		Total)	on
4)	0.308)		6)			0.128)	<u>ω</u>				0.125)				5)									17)											
	Cancer Inflam	Cell P	Inflam	Cancer		Cell P	Inflam	Cancer				Trauma	Inflam	Cancer	Cell P	Inflam	Cancer	Cell P	Inflam	Cancer	Inflam	Cell P	Cancer	Cell P	Inflamu	Cancer	Cell P	Inflam	Cancer	Cell p	Cancer	(0.371)	Inflam	Fraction of	Disease
	Cancer (0.538) Inflammation (0	Cell Proliferation	Inflammation (0.238)	Cancer (0.483)		Cell Proliferation	Inflammation (0	(0.429)				Trauma (0.250)	Inflammation (0	(0.375)	Cell Proliferat	Inflammation (0	Cancer (0.432)	Cell Proliferation	Inflammation (0.381)	Cancer (0.238)	Inflammation (0.160)	Cell Proliferation (0.480)	(0.480)	Cell Froliferation (0.162)	Inflammation (0	Cancer (0.500)	Cell Proliferation (0.167)	Inflammation (0	Cancer (0.461)	Cell proliferation	Cancer (0.333)		Inflammation/Trauma	on of T	유
	) (0.308)	ion	(0.238)				(0.270)					_	(0.375)		ion	(0.259)			(0.381)	_	(0.160)	ation (	_	ation (	(0.176)		ation (	(0.180)			_		Trauma	Total	Condition
		(0.161)				(0.186)									(0.154)			(0.190)				0.480)		0.162)			0.167)			(0.141)					
	PINCY		1	DINCY				DINCY			•			PSPORT1		-	PINCY			PSPORT1			PBLUESCRIPT		-	PBLUESCRIPT			PBLUESCRIPT				PINCY	•	Vector
														7						1			CRIPT			CRIPT			CRIPT						

Table 3 (cont.)

	Cell Proliferation(U.132)	Gastrointestinal (0.145)		
	Cancer (0.355)	0		
PINCY	Inflammation (0.368)	Hematopoietic/Immune (0.250)	465-509	96
	Cell Proliferation(0.212)	Nervous (0.173)		
		Gastrointestinal (0.192)		
PINCY	Cancer (0.481)	Reproductive (0.192)	1173-1217	95
	Inflammation (0.103)	Developmental (0.138)		
	Cell Proliferation(0.241)	Nervous (0.241)		
PBLUESCRIPT	Cancer (0.414)	Reproductive (0.379)	126-170	94
	Trauma (0.188)			
	Inflammation (0.188)	Developmental (0.125)		
	Cell Proliferation(0.281)	Hematopoietic/Immune (0.156)		
PSPORT1	er (0.312)	Reproductive (0.219)	761-805	93
	Cell Proliferation(0.160)	Gastrointestinal (0.123)		
	Inflammation (0.189)	Nervous (0.217)		
PSPORT1	Cancer (0.481)	Reproductive (0.274)	489-533	92
	Cell Proliferation(0.211)	Gastrointestinal (0.158)		
	Inflammation (0.263)	Reproductive (0.197)		
PSPORT1	Cancer (0.461)	Nervous (0.211)	72-116	91
	Cell Proliferation(0.123)	Hematopoietic/Immune (0.158)		
	Inflammation (0.211)	Reproductive (0.193)	879-923	
PINCY	Cancer (0.439)	Nervous (0.316)	69-113	90
		Developmental (0.111)		
	Cell Proliferation(0.333)	Hematopoietic/Immune (0.111)		
	Inflammation (0.333)	Nervous (0.222)	352-396	
PINCY	Cancer (0.444)	Reproductive (0.556)	184-228	89
	Trauma (0.137)	Gastrointestinal (0.168)		
	Inflammation (0.298)	Reproductive (0.214)		
PINCY	Cancer (0.397)	Nervous (0.237)	139-183	88
	Trauma (0.115)			
	Cell Proliferation (0.115)	Hematopoietic/Immune (0.115)		
•	Inflammation (0.192)	Gastrointestinal (0.250)		
PINCY	Cancer (0.558)	Reproductive (0.250)	117-161	87
	Cell Proliferation (0.157)	Nervous (0.169)		
	Inflammation (0.193)	Cardiovascular (0.181)		
PINCY	Cancer (0.434)	Reproductive (0.277)	238-282	86
			Fragments	SEQ ID NO:
Vector	Disease or Condition	Tissue Expression	Selected	Nucleotide

able 3 (cont.)

107 1 8 1	106 2 5	105	104 4	103 1	102 8	101 8	100		98 2		Nucleotide S SEQ ID NO: F
167-211 814-859 1922-1966	255-299 513-557		413-457 908-952	199-243	8-52	861-905	/3-11/ 460-504	106-150	23-67	2427-2471	Selected Fragments
Reproductive (0.263) Nervous (0.162) Gastrointestinal (0.141)	Reproductive (0.216) Gastrointestinal (0.196) Nervous (0.157)	Reproductive (0.270) Gastrointestinal (0.169) Hematopoietic/Immune 0.101) Developmental (0.101) Nervous (0.101)	Nervous (0.236) Reproductive (0.222) Gastrointestinal (0.125)	Hematopoietic/Immune (0.143) Nervous (0.179) Reproductive (0.286)	Developmental (1.000)	Developmental (0. 333) Nervous (0.667)	Hematopoletic/Immune (0.211) Reproductive (0.211) Cardiovascular (0.105) Developmental (0.105) Gastrointestinal (0.105) Musculoskeletal (0.105)	2	Gastrointestinal (0.270) Reproductive (0.190) Cardiovascular (0.135)	Nervous (0.224) Reproductive (0.197) Gastrointestinal (0.184)	Tissue Expression (Fraction of Total)
Cancer (0.455) Inflammation (0.202) Trauma (0.131)	Cancer (0.490) Inflammation (0.176) Cell Proliferation(0.176)	Cancer (0.449) Inflammation (0.281) Cell Proliferation(0.258)	Cancer (0.458) Inflammation (0.236) Cell Proliferation(0.139)	Cancer (0.536) Inflammation (0.250) Cell Proliferation(0.214)	Cell Proliferation (1.000)	Cell Proliferation(0. 333) Trauma (0. 333) Neurological (0.333)	Cancer (0.4/4) Inflammation (0.263) Cell Proliferation(0.211)		Cancer (0.429) Inflammation (0.278) Cell Proliferation(0.143)	Cancer (0.474) Cell Proliferation(0.263) Inflammation (0.237)	Disease or Condition Fraction of Total
PINCY	PINCY	PINCY	PINCY	PINCY	PINCY	PINCY	H TAOPORT	PINCY	PINCY	ÞINCY	Vector

Table 3 (cont.)

Nucleotide   Selected	Selected	Tissue Expression	Disease or Condition	Vector
SEQ ID NO: Fragments	Fragments	(Fraction of Total)	Fraction of Total	
108	877-921	Reproductive (0.299)	Cancer (0.536)	PINCY
, .	2230-2274	Nervous (0.206)	Inflammation (0.227)	
		Gastrointestinal (0.134)	Cell Proliferation(0.124)	

		15	001	, , , , , , , , , , , , , , , , , , ,	<u> </u>	<del></del>	
61	60	59	58	57	56	55	Nucleotide SEQ ID NO:
LIVRTUT01	LNODNOT03	SPLNNOT04	BRAINOT12	PLACNOT02	BRSTNOT02	KIDNNOT01	Library
Library was constructed using RNA isolated from liver tumor tissue removed from a 51- year-old Caucasian female during a hepatic lobectomy. Pathology indicated metastatic	Library was constructed using RNA isolated from lymph node tissue obtained from a 67-year-old Caucasian male during a segmental lung resection and bronchoscopy. On microscopic exam, this tissue was found to be extensively necrotic with 10% viable tumor. Pathology for the associated tumor tissue indicated invasive grade 3-4 squamous cell carcinoma. Patient history included hemangioma. Family history included atherosclerotic coronary artery disease, benign hypertension, congestive heart failure, atherosclerotic coronary artery disease.	Library was constructed using RNA isolated from the spleen tissue of a 2-year-old Hispanic male, who died from cerebral anoxia.	Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. Family history included a cervical neoplasm.	Library was constructed using RNA isolated from the placental tissue of a Hispanic female fetus, who was prematurely delivered at 21 weeks' gestation. Serologies of the mother's blood were positive for CMV (cytomegalovirus).	Library was constructed using RNA isolated from diseased breast tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated proliferative fibrocysytic changes characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Pathology for the associated tumor tissue indicated an invasive grade 4 mammary adenocarcinoma. Patient history included atrial tachycardia and a benign neoplasm. Family history included cardiovascular and cerebrovascular disease.	Library was constructed using RNA isolated from the kidney tissue of a 64-year-old Caucasian female, who died from an intracranial bleed. Patient history included rheumatoid arthritis.	Library Description

### able 4 (cont.)

		101				(0 7
68	67	66	65	64	62	Nucleotide SEQ ID NO:
LNODNOT11	PROSTUT13	TESTNOT07	LUNGNOT23	LIVRFET02	BLADTUT07	Library
Library was constructed using RNA isolated from lymph node tissue removed from a 16-month-old Caucasian male who died from head trauma. Patient history included bronchitis.	Library was constructed using RNA isolated from prostate tumor tissue removed from a 59-year-old Caucasian male during a radical prostatectomy with regional lymph node excision. Pathology indicated adenocarcinoma (Gleason grade 3+3). Adenofibromatous hyperplasia was present. The patient presented with elevated prostate-specific antigen (PSA). Patient history included colon diverticuli, asbestosis, and thrombophlebitis. Family history included multiple myeloma, hyperlipidemia, and rheumatoid arthritis	Library was constructed using RNA isolated from testicular tissue removed from a 31-year-old Caucasian male during an unilateral orchiectomy (excision of testis). Pathology indicated a mass containing a large subcapsular hematoma with laceration of the tunica albuginea. The surrounding testicular parenchyma was extensively necrotic.	Library was constructed using RNA isolated from left lobe lung tissue removed from a 58-year-old Caucasian male. Pathology for the associated tumor tissue indicated metastatic grade 3 (of 4) osteosarcoma. Patient history included soft tissue cancer, secondary cancer of the lung, prostate cancer, and an acute duodenal ulcer with hemorrhage. Family history included prostate cancer, breast cancer, and acute leukemia.	Caucasian male, who died from head trauma. Patient history included asthma.  Library was constructed using RNA isolated from liver tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.	from blad casian mal chology in Patient included in type II	Library Description

### able 4 (cont.)

	Nucleotide SEQ ID NO:	Library BRSTNOT35	Library Description Library was constru old Caucasian femal
	(		old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated normal breast parenchyma, bilaterally. The patient presented with hypertrophy of breast and headache. Patient history included obesity, lumbago, glaucoma, and alcohol abuse. Family history included cataract, osteoarthritis, uterine cancer, benign hypertension, hyperlipidemia, alcoholiccirrhosis of the liver, cerebrovascular disease, and type II diabetes.
	70	MUSCNOT01	was c
	71	LUNGNOT1 4	Library was constructed using RNA isolated from lu lower lobe of a 47-year-old Caucasian male during Pathology for the associated tumor tissue indicate parenchyma showed calcified granuloma. Patient his and chronic obstructive pulmonary disease. Family and acute myocardial infarction.
. 701	72	UTRSNOT06	Library was constructed using RNA isolated from myometrial tissue removed from a 50-year-old Caucasian female during a vaginal hysterectomy. Pathology indicated residual atypical complex endometrial hyperplasia. Pathology for the associated tissue removed during dilation and curettage indicated fragments of atypical complex hyperplasia and a single microscopic focus suspicious for grade 1 adenocarcinoma. Patient history included benign breast neoplasm, hypothyroid disease, polypectomy, and arthralgia. Family history included cerebrovascular disease, atherosclerotic coronary artery disease, hyperlipidemia, and chronic hepatitis.
	73	PROSTUT08	
	74	THYMNOT03	Library was constructed using RNA isolated from thymus tissue removed from a 21-yea old Caucasian male during a thymectomy. Pathology indicated an unremarkable thymus and a benign parathyroid adenoma in the right inferior parathyroid. Patient history included atopic dermatitis, a benign neoplasm of the parathyroid, and tobacco use. Family history included atherosclerotic coronary artery disease and benign hypertension.

			101				
82	81	80	79	77	76	75	Nucleotide SEQ ID NO:
PROSNON01	BRAITUT08	BRAINOT04	HNT2RAT01	HUVELPB01	BRAUNOT01	PENCNOT01	Library
This library was constructed from 4.4 million independent clones from a prostate library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male who died from a self-inflicted gunshot wound. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period.	A isolated from brain tumor d Caucasian male during exc. grade 4 fibrillary astrocy y included cerebrovascular of family history included cere	This library was constructed using RNA isolated from the brain tissue of a 44-year-old Caucasian male with a cerebral hemorrhage. The tissue, which contained coagulated blood, came from the choroid plexus of the right anterior temporal lobe. Family history included coronary artery disease and myocardial infarction.	library was constructed at Stratagene (STR9 cell line (derived from a human teratocarci acteristic of a committed neuronal precursor for 24 hours.	This library was constructed using RNA isolated from HUV-EC-C (ATCC CRL 1730) cells stimulated with cytokine/LPS. RNA was isolated from two pools of HUV-EC-C cells that had been treated with either 4 units/ml TNF-alpha and 2 units/ml gamma IFN for 96 hours, or 1 unit/ml IL-1 beta and 100 ng/ml LPS for 5 hours.  This library was constructed using RNA isolated from HUV-EC-C (ATCC CRL 1730) cells.	Library was constructed using RNA isolated from caudate/putamen/nucleus accumbens tissue removed from the brain of a 35-year-old Caucasian male who died from cardiac failure. Pathology indicated moderate leptomeningeal fibrosis and multiple microinfarctions of the cerebral neocortex. Patient history included dilated cardiomyopathy, congestive heart failure, cardiomegaly and an enlarged spleen and liver.	Library was constructed using RNA isolated from penis corpus cavernosum tissue removed from a 53-year-old male. Patient history included untreated penile carcinoma.	Library Description

•	89	88	87	<del>*************************************</del>	85			w z
S	•	8	7	o	5	4	83	Nucleotide SEQ ID NO:
CKIND IMO1	LUNGFET03	SINTNOT13	SINTNOT13	PROSNOT16	STOMFET01	BRAITUT13	PANCTUT01	Library
Caucasian female fetus, who died at 20 weeks' gestation.	ary was constructed using RNA isolate	This library was constructed using RNA isolated from ileum tissue obtained from a 25-year-old Asian female during a partial colectomy and temporary ileostomy. Pathology indicated moderately active chronic ulcerative colitis, involving colonic mucosa from the distal margin to the ascending colon. Family history included hyperlipidemia, depressive disorder, malignant cervical neoplasm, viral hepatitis A, and depressive disorder.	This library was constructed using RNA isolated from ileum tissue obtained from a 25-year-old Asian female during a partial colectomy and temporary ileostomy. Pathology indicated moderately active chronic ulcerative colitis, involving colonic mucosa from the distal margin to the ascending colon. Family history included hyperlipidemia, depressive disorder, malignant cervical neoplasm, viral hepatitis A, and depressive disorder.	This library was constructed using RNA isolated from diseased prostate tissue removed from a 68-year-old Caucasian male during a radical prostatectomy. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). The patient presented with elevated prostate specific antiger (A). During this hospitalization, the patient was diagnosed with myasthenia gravia. Patient history included osteoarthritis and type II diabetes. Family history included benign hypertension, acute myocardial infarction, hyperlipidemia, and arteriosclerotic coronary artery disease.	This library was constructed using RNA isolated from the stomach tissue of a Caucasian female fetus, who died at 20 weeks' gestation.	This library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 68-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a meningioma in the left frontal lobe.	This library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.	Library Description

## Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Description
91	LUNGTUT03	This library was constructed using RNA isolated from lung tumor tissue removed from the left lower lobe of a 69-year-old Caucasian male during segmental lung resection. Pathology indicated residual grade 3 invasive squamous cell carcinoma. Patient history included acute myocardial infarction, prostatic hyperplasia, malignant skin neoplasm, and tobacco use.
 92	OVARTUT01	This library was constructed using RNA isolated from ovarian tumor tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology indicated grade 2 mucinous cystadenocarcinoma involving the entire left ovary. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.
 93	LUNGFET05	This library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation from anencephalus.
94	ENDANOT01	This library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
95	ESOGTUT02	This library was constructed using RNA isolated from esophageal tumor tissue obtained from a 61-year-old Caucasian male during a partial esophagectomy, proximal gastrectomy, pyloromyotomy, and regional lymph node excision. Pathology indicated an
· !		atherosclerotic coronary artery disease, type II diabetes, chronic liver disease primary cardiomyopathy, benign hypertension, and cerebrovascular disease.
96	SINIUCT01	This library was constructed using RNA isolated from ileum tissue obtained from a year-old Caucasian male during a total intra-abdominal colectomy and endoscopic jejunostomy. Previous surgeries included polypectomy, colonoscopy, and spinal cana exploration. Family history included cerebrovascular disease, benign hypertension, atherosclerotic coronary artery disease, and type II diabetes.
97	NPOLNOT01	This library was constructed using RNA isolated from nasal polyp tissue removed from a 78-year-old Caucasian male during a nasal polypectomy. Pathology indicated a nasal polyp and striking eosinophilia. Patient history included asthma and nasal polyps.
98	ADRENOT09	This library was constructed using RNA isolated from left adrenal gland tissue removed from a 43-year-old Caucasian male during nephroureterectomy, regional lymph node excision, and unilateral left adrenalectomy. Pathology for the associated tum tissue indicated a grade 2 renal cell carcinoma mass in the posterior lower pole of the left kidney with invasion into the renal pelvis.

# Table 4 (cont.)

201
PLACFEROL
Inis library was constructed using RNA isolated from placental tissue removed from a Caucasian fetus who died after 16 weeks' gestation from fetal demise and hydrocephalus. Serology was positive for CMV antibody.

### Table 4 (cont.)

Nucleotide Library Library Description  SEQ ID NO:  This library was constructed using RNA isolated from posterior parion of a 35-year-old Caucasian male.  This library was constructed using RNA isolated from fallopian tube removed from an 85-year-old Caucasian female during bilateral salpi and hysterectomy. Pathology indicated poorly differentiated mixed eserous adenocarcinoma confined to the mucosa without mural involven carcinoma in situ was also present. Pathology for the associated ut indicated focal endometrioid adenocarcinoma in situ and moderately invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinom avere present. The patient presented with a pelvic main farction.			
BRAENOT02 FTUBTUT02	Nucleotide L	ibrary	Library Description
FTUBTUT02	—	RAENOT02	This library was constructed using RNA isolated from posterior parietal cortex tissue
FTUBTUT02			removed from the brain of a 35-year-old Caucasian male.
removed from an 85-year-old Caucasian female during bilateral salpi and hysterectomy. Pathology indicated poorly differentiated mixed e serous adenocarcinoma confined to the mucosa without mural involven carcinoma in situ was also present. Pathology for the associated ut indicated focal endometrioid adenocarcinoma in situ and moderately invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic map atient history included medullary carcinoma of the thyroid and myclinfarction.			This library was constructed using RNA isolated from fallopian tube tumor tissue
and hysterectomy. Pathology indicated poorly differentiated mixed e serous adenocarcinoma confined to the mucosa without mural involven carcinoma in situ was also present. Pathology for the associated ut indicated focal endometrioid adenocarcinoma in situ and moderately invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic material polypatient history included medullary carcinoma of the thyroid and myclinfarction.			removed from an 85-year-old Caucasian female during bilateral salpingo-oophorectomy
serous adenocarcinoma confined to the mucosa without mural involven carcinoma in situ was also present. Pathology for the associated ut indicated focal endometrioid adenocarcinoma in situ and moderately invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic material polype. The patient history included medullary carcinoma of the thyroid and myconfinity infarction.		,	and hysterectomy. Pathology indicated poorly differentiated mixed endometrioid and
carcinoma in situ was also present. Pathology for the associated ut indicated focal endometrioid adenocarcinoma in situ and moderately invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic material polype attent history included medullary carcinoma of the thyroid and myclinfarction.			serous adenocarcinoma confined to the mucosa without mural involvement. Endometrioid
indicated focal endometrioid adenocarcinoma in situ and moderately invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic map attent history included medullary carcinoma of the thyroid and myconfarction.			carcinoma in situ was also present. Pathology for the associated uterus tumor
invasive adenocarcinoma in an endometrial polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic material polyp. Metastatic endomet adenocarcinoma were present. The patient presented with a pelvic material polyp. Metastatic endometrial endometria			indicated focal endometrioid adenocarcinoma in situ and moderately differentiated
adenocarcinoma were present. The patient presented with a pelvic material patient history included medullary carcinoma of the thyroid and myclinfarction.			invasive adenocarcinoma in an endometrial polyp. Metastatic endometrioid and serous
Patient history included medullary carcinoma of the thyroid and myc			adenocarcinoma were present. The patient presented with a pelvic mass and ascites.
infarction.	<u>.                                     </u>		Patient history included medullary carcinoma of the thyroid and myocardial
			infarction.

ABI AutoAssembler

A program that assembles nucleic acid sequences.

PE Biosystems, Foster City, CA.

sequence against those in BLOCKS, PRINTS,

DOMO, PRODOM, and PFAM databases to search

for gene families, sequence homology, and structural

fingerprint regions.

A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.  FDF A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Program	Description	Reference	Parameter Threshold
A Fast Data Finder useful in comparing and PE Biosystems, Foster City, CA; annotating amino acid or nucleic acid sequences. Paracel Inc., Pasadena, CA.	ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	PE Biosystems, Foster City, CA.	
	ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	PE Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%

	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group c sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	BLAST  A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tbl:
A BLocks IMProved Searcher that matches a	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.
Henikoff, S. and J.G. Henikoff (1991) Nucleic Score=1000 or greater;	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.
Score=1000 or greater;	ESTs: fasta E value=1.06E-6  Assembled ESTs: fasta Identity= 95% or greater and  Match length=200 bases or greater; fastx E value=1.0E-8 or less  Full Length sequences: fastx score=100 or greater	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less

Chem. Inf. Comput. Sci. 37:417-424.

266:88-105; and Attwood, T.K. et al. (1997) J. S. Henikoff (1996) Methods Enzymol. Acids Res. 19:6565-6572; Henikoff, J.G. and

What is claimed is:

I. An isolated polypeptide comprising an amino acid sequence selected from the group

consisting of:

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and SEQ ID NO:54,

SEQ ID NO:53, and SEQ ID NO:54,

- a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID
- b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, S
- consisting of SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34, SEQ ID NO:43, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:37, SEQ ID NO:37, SEQ ID NO:33, SEQ ID NO:37, SEQ ID NO:37, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:36, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:37
- of SEQ ID NO:7, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:17, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:19, SEQ ID NO:19, SEQ ID NO:10, SEQ ID NO:10,

## Table 5 (cont.)

Motifs	SPScan	Consed	Phrap	Phred	ProfileScan	Program
A program that searches amino acid sequences for patterns that matched those defined in Prosite.	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	A graphical tool for viewing and editing Phrap assemblies.	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Description
Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Reference
	Score=3.5 or greater		Score= 120 or greater; Match length= 56 or greater		Normalized quality score>GCG- specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.	Parameter Threshold

NO:31, SEQ ID NO:22, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:33, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:36, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO

- 2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:3, SEQ ID
- 3. An isolated polynucleotide encoding a polypeptide of claim 1.
- 20 4. An isolated polynucleotide encoding a polypeptide of claim 2.
- 5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:57, SEQ ID NO:57, SEQ ID NO:57, SEQ ID NO:67, SEQ ID NO:67, SEQ ID NO:67, SEQ ID NO:77, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:77, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:77, SEQ ID NO:87, SEQ ID NO:77, SEQ ID NO:97, SEQ ID
- 6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
- 35 7. A cell transformed with a recombinant polynucleotide of claim 6.

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8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

- 9. A method for producing a polypeptide of claim 1, the method comprising:
- a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim
- b) recovering the polypeptide so expressed.
- 10. An isolated antibody which specifically binds to a polypeptide of claim 1.
- 11. An isolated polynucleotide comprising a polynucleotide sequence selected from the
- a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:67, SEQ I
- b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:67, SEQ ID NO:77, SE
- c) a polynucleotide sequence complementary to a),
- d) a polynucleotide sequence complementary to b), and
- e) an RNA equivalent of a)-d).

SEQ ID NO: 107, and SEQ ID NO: 108,

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group consisting of:

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12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a

polynucleotide of claim 11.

- 13. A method for detecting a target polynucleotide in a sample, said target polynucleotide
- having a sequence of a polynucleoude of claim 11, the method comprising:

  a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides
- comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and
- b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.
- 14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.
- 15. A method for detecting a target polynucleotide in a sample, said target polynucleotide
- a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction
- amplification, and

  b) detecting the presence or absence of said amplified target polynucleotide or fragment
- 20 thereof, and, optionally, if present, the amount thereof.

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- l6. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.
- IN. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO
- 35 18. A method for treating a disease or condition associated with decreased expression of

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functional CCYPR, comprising administering to a patient in need of such treatment the composition of claim 16.

- 19. A method for screening a compound for effectiveness as an agonist of a polypeptide of S claim 1, the method comprising:
- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting agonist activity in the sample.
- 20. A composition comprising an agonist compound identified by a method of claim 19 and 10 a pharmaceutically acceptable excipient.
- 21. A method for treating a disease or condition associated with decreased expression of functional CCYPR, comprising administering to a patient in need of such treatment a composition of claim 20.
- 22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:
- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

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- 23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.
- 24. A method for treating a disease or condition associated with overexpression of functional 23. CCYPR, comprising administering to a patient in need of such treatment a composition of claim 23.
- 25. A method of screening for a compound that specifically binds to the polypeptide of claim I, said method comprising the steps of:
- a) conditions, and combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a
- compound that specifically binds to the polypeptide of claim 1.
- 35 claim 1, said method comprising:

26. A method of screening for a compound that modulates the activity of the polypeptide of

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s) combining the polypeptide of claim I with at least one test compound under conditions

- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound,
- compound that modulates the activity of the polypeptide of claim 1 in the presence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.
- 27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:
- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.
- 28. A method for assessing toxicity of a test compound, said method comprising:
- a) treating a biological sample containing nucleic acids with the test compound;
- b) hybridization complex is formed between said probe and a target polynucleotide in the biological hybridization complex is formed between said probe and a target polynucleotide in the biological
- 20 hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim
- c) quantifying the amount of hybridization complex; and

11 or fragment thereof;

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and

- d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the
- amount of hybridization complex in the treated biological sample, wherein a difference in the test amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

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#1. Menlo Park, CA 94025 (US). SHAH, Purvi [IN/US]; PATTERSON, Chandra [US/US]; 490 Sherwood Way 14244 Santiago Road, San Leandro, CA 94577 (US). Jose, CA 95123 (US). BAUGHN, Mariah, R. [US/US]; (US). LU, Dyung, Aina, M. [US/US]; 233 Coy Drive, San Junming [CN/US]: 7125 Bark Lane, San Jose, CA 95129 Canyon Drive, Castro Valley, CA 94552 (US). YANG,

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UG, US, UZ, VN, YU, ZA, ZW. RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, LY, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, IN' 12' 115' RE' KG' KB' KK' KZ' TC' TK' TK' T2' TL' TN' DW' EE' E2' H' GB' GD' GE' GH' GW' HB' HN' ID' IT' BY' BB' BG' BK' BX' CY' CH' CN' CK' CN' CS' DE' DK' (18) Designated States (national): AE, AL, AM, AT, AU, AZ,

CI' CW' GY' GN' GM' MT' MK' NE' 2N' LD' LG). IT. LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, patent (AT, BE, CH, CY, DE, DK, ES, Fl, FR, GB, GR, IE, patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian (84) Designated States (regional): ARIPO patent (GH. CM.

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Alto, CA 94304 (US). CENOMICS, INC. [US/US]; 3160 Porter Drive, Palo (71) Applicant (for all designated States except US): INCYTE

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(54) Title: CELL CYCLE AND PROLIFERATION PROTEINS

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**AO1K67/027** CO7K16/18 CO1KI4/47 VELY CIZNIS/IN GOIN33/50 P. CLASIFICATION OF SUBJECT MATTER ASSISTANCE OF

According to International Patent Classification (IPC) or to both national classification and IPC

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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## INTERNATIONAL SEARCH REPORT

No protest accompanied the payment of additional search feet	
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see further information sheet invention group 1.	
No required additional search fees were timely paid by the applicant. Consequently, this International Search Reportesticted to the invention first mentioned in the claims; it is covered by claims Nos.:	<b>,</b>
As only some of the required additional search fees were timely paid by the applicant, this International Search Re covers only those claims for which fees were paid, specifically claims Nos.:	3. [
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite part any additional fee.	s. [
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.	] 1
International Searching Authority found multiple inventions in this international application, as follows:	eidT
International Searching Authority found multiple inventions in this international application, as follows:	
Decause they are dependent claims and are not drafted in accordance with the second and third sentences of Ruck II Observations where unity of invention is lacking (Continuation of item 2 of first sheet) International Searching Authority found multiple inventions in this international application, as follows:	8
because they relate to parts of the International Application that do not comply with the prescribed requirements is nextent that no meaningful international Search can be carried out, specifically:  Claims Mos.:  Decause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rubecause they are dependent claims and are not drafted in accordance.	3.

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